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EMCDDA PROJECT

"REVIEW OF SCIENTIFIC STUDIES OF MORTALITY AMONG DRUG USERS AND FEASIBILITY STUDY FOR A COMMON METHODOLOGY FOR MONITORING OVERALL AND CAUSE-SPECIFIC MORTALITY AMONG DRUG USERS IN MEMBER STATES"

FINAL REPORT

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THE ORGANIZATION AND MANAGEMENT OF THIS PROJECT HAS BEEN CARRIED OUT BY:

EPI - ASSOCIAZIONE ITALIANA PER LA RICERCA IN EPIDEMIOLOGIA

See also “LIST OF PARTICIPANTS” in Annex 1

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Preface

The project was developed according to the following phases:

1. Collection of published studies on mortality among drug users.
2. Critical revision of the methods used and the results obtained in the selected studies.
3. Oganization of a meeting to discuss the major issues to be taken into account for developing a standardized methodology to assess overall and cause-specific mortality rates among drug users in Member States of European Union.
4. Draft of a standardized protocol for a cohort mortality study among drug users in different European Countries.

LITERATURE REVIEW OF SCIENTIFIC STUDIES ON OVERALL AND CAUSE SPECIFIC MORTALITY AMONG DRUG USERS

Introduction

1. Source of mortality data

Mortality data can be generated from two basic types of study:

a) cross-sectional studies

b) longitudinal studies

The cross-sectional studies measure all drug-related deaths occurring in a particular area and in a specific period of time. The value of this kind of study mainly depends on the accuracy in identifying addict deaths and specifying both the criteria of classification of drug-related death and the source of data.

In longitudinal studies, a specific group of addicts (generally enrolled at treatment centres) is followed over a definite time period of years. This kind of studies provides accurate data on the outcome of addiction within a particular group and it is the only one that allows to estimate the actual overall and cause-specific mortality rates.

2. Data on drug related deaths: problems of definition

In most European countries different sources of data on drug-related deaths are available, such as public health authorities, the police or the judiciary, and yield annual figure. It is, however, debatable whether they can be used to describe the extent and pattern of drug-related deaths in each countries and whether these figures are comparable because of the lack of both consensus regarding the definition that should be applied to such deaths and a common classification. The criteria for the definition of "drug-related death" can be based on:

(a) clinical and toxicological criteria, such as the type of substance used and the route of administration;

(b) the circumstances surrounding the death;

(c) person known as a drug addict.

Different European countries places emphasis on the various aspects of these criteria and consequently the definitions of drug-related death adopted in various countries may differ. Moreover, epidemiological assessment of drug-related deaths may even be difficult within a given country because data from different sources (i.e. death certificates or records of a ministry of health and a ministry of justice) can produce very different estimates.

Different types of death can be considered as "drug-related" and the following is only one of the possible classifications:

deaths due to massive intoxications or overdoses

suicide related to drug dependence

deaths due to accidents and violence influenced by drug use

deaths due to long-term abuse of drugs

deaths due to behaviour associated with drug use

Although most European countries have national and/or regional mortality registers where deaths are coded on the basis of the International Classification of Disease (ICD), the heterogeneity of "cause" of death definition and, consequently, of the codes applied, make it difficult to compare consistent estimates of deaths among drug users.

3. Mortality of Drug Users: determinants of estimates

Different factors can affect the estimate of mortality of drug users (figure 1).

The first step should be *the identification of the actual population of drug users* out of the overall population. The use of psychotropic drugs in Europe is an illicit behaviour, even though with different levels of tolerance, therefore drug users can be considered a hidden population. The available observation systems only allow to identify drug users referring to health services for either treatment for drug abuse or health problems related to their drug use. Therefore, different variables affects the likelihood of identifying drug users:

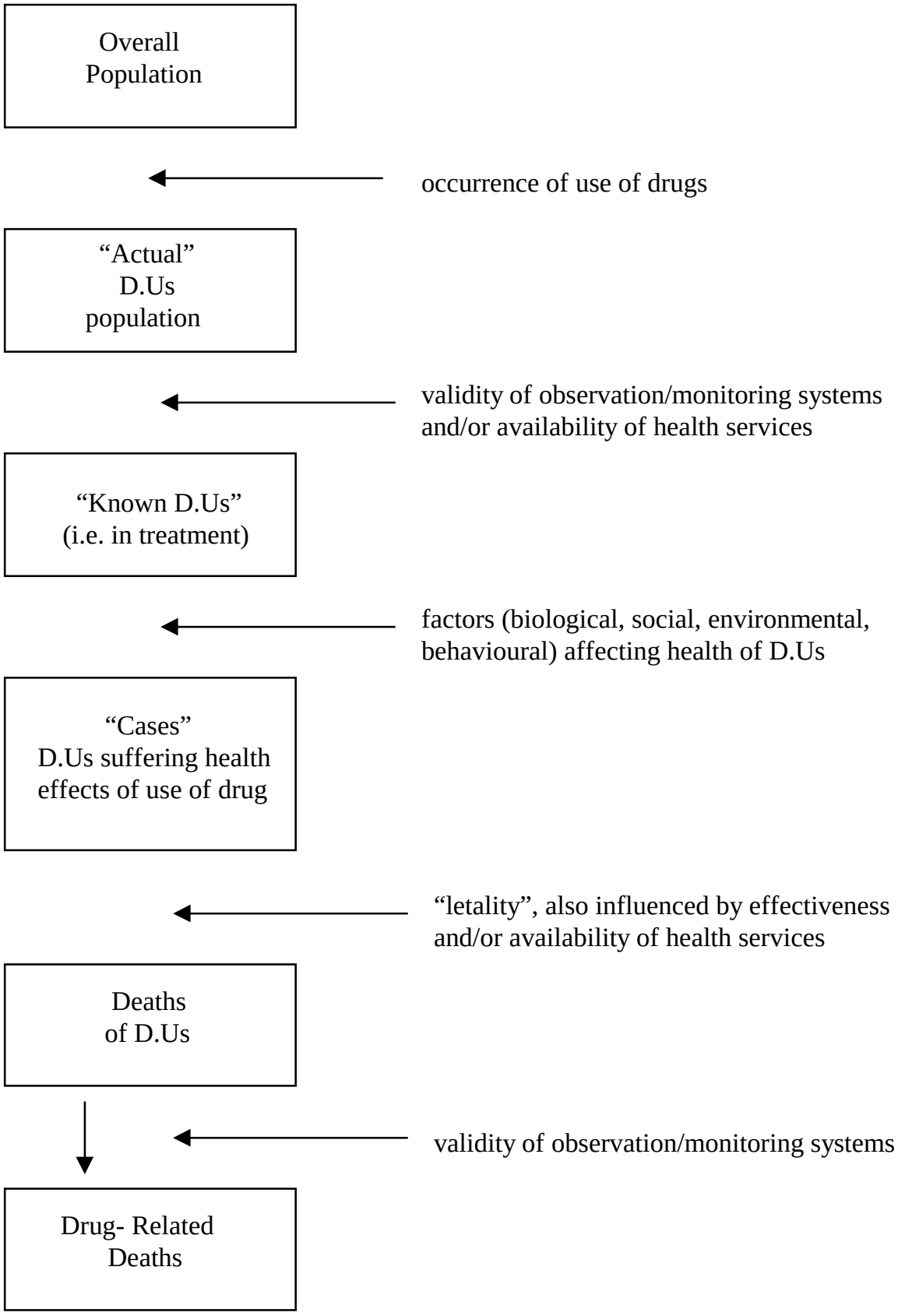
a) the potential for harm of the drug used, itself depending on biological, social, environmental and behavioral factors;
b) the availability of health services;
c) the accessibility and acceptance of health services.

The second step is the identification of deaths among drug users. Mortality of drug users depends on both prevalence of drug users and lethality. Determinants of prevalence have been already discussed. Lethality of drug users is affected by:

a) the actual harm of drug use
b) the availability of health services
c) the effectiveness of health services.

The identification of deaths among drug users depends on the available monitoring systems. Most of them measure deaths directly related to drug use without a standard definition of "case" not only across countries but also within countries. Furthermore, the national mortality monitoring systems, although using standardized methods to measure causes of deaths, do not provide a specific code for deaths occurring among drug users.

Figure 1


Overall Population
occurrence of use of drugs
"Actual" D.Us population
validity of observation/monitoring systems and/or availability of health services
"Known D.Us" (i.e. in treatment)
factors (biological, social, environmental, behavioural) affecting health of D.Us
"Cases" D.Us suffering health effects of use of drug
"letality", also influenced by effectiveness and/or availability of health services
Deaths of D.Us
validity of observation/monitoring systems
Drug- Related Deaths

Eventually, what is usually available is the number of drug-related deaths over the general population.

This indicator might be heavily biased, both in geographical and temporal comparisons, by the following factors:

- heterogeneity of occurrence of drug use
- heterogeneity of determinants of health of drug users
- heterogeneity of effectiveness and/or availability of health services
- heterogeneity and/or validity of "case definition" of drug-related death

Sometimes estimates are provided of "rates" of drug-related death over the observed population of drug users, using estimates of both numerator and denominator coming from independent sources. In other terms it is not satisfied the condition that cases (deaths) must come from the study population; the latter indicator , therefore, cannot represent a valid estimate of mortality of drug users.

4. To estimate overall and cause-specific mortality rates among drug users

Most of knowledge available on mortality of drug users comes from measure of directly and indirectly drug-related deaths, in terms of rate over the general population but only longitudinal studies can measure the actual mortality rate among drug users. This is a major epidemiological task because reliable data are difficult to gather.

Mortality in the general population is currently measured; the denominator is an estimate of the resident population in a defined time and place and the numerator is the corresponding number of deaths. The requirements for measuring mortality rates in the general population are:

the availability of an estimate of resident population at mid-time;

a comprehensive ascertainment of vital status for the corresponding period;

coding of causes of death.

The requirements needed to estimate mortality among overall and actual population of drug users are both missing. We do not have currently both measures:

a) the size of the resident population of drug users
b) comprehensive ascertainment of vital status

As far as the latter issue is concerned, there is no code of the International Classification of Diseases specific for intravenous use of drugs; therefore it is only possible to measure deaths classified as those relating to drug dependence (ICD IX: 309) or among those relating to injury and poisoning (ICD IX: 965). We have already stated that different sources of data for overdose deaths are available, but their validity is extremely heterogeneous over time and space. For instance, official

reports from hospitals or medical examiner offices are incomplete in their coverage of drug related incidents. Another limitation of using "drug-related" deaths to approximate mortality of drug users, comes from the evidence that drug users do actually die also from other causes. The proportion of deaths coded as death due to drug dependence and poisoning by opiates and related narcotics - respectively ICD IX 304.0-304.9 and 965.0 - out of the total deaths, estimated in a multicentric cohort study on mortality of drug injectors, ranged from 0 in New Haven to 46.7% in Liverpool during the period 1980-1992.

In conclusion, mortality cohort study can be considered the most valid and reliable study design to investigate the health effects of drug abuse and their heterogeneity.

Some limitations of longitudinal studies must be considered:

the study population is always a "selected" group of known drug users. It can not be excluded that the selection factors for including in the cohort population could be themselves determinants of mortality. Maximum effort must be made to check whether the study population can be considered representative of the actual population of drug users.

mortality rates of causes of death/diseases which are amenable for medical and/or emergency treatment can be seriously biased, in time and space comparisons, by the heterogeneous availability and/or effectiveness of health services

limitation of extent and duration of follow-up and proportion of drug users lost to follow-up could bias the mortality estimates.

Moreover, specific attention must be paid in adopting procedures and methods to protect privacy of drug users.

Methods and results

Published studies on mortality among drug users were identified through computerized searches (*MEDLARS databases*) from January 1980 till December 1996, using the subject headings of:

narcotic dependence ***or*** *substance abuse / mortality* ***or*** *overdose / mortality, epidemiology epidemiology epidemiology epidemiology epidemiology mortality,epidemiologh epidemiology* epidemiology

Also, a handsearch of the studies published before 1980, has been conducted following the references in the papers selected through the computerized searches. The latter method have not yield an exhaustive list of papers on mortality of drug users, but we have traced the most quoted and significant papers published between 1965 and 1979. Searches were limited to English language publications.

Out of 340 papers that were identified, 66 have been selected to be reviewed because of

their relevance for the project. A total of 20 papers dealing with studies carried out in countries outside Europe have been included because of their particular significance. Letters, editorials and reports have been also included because of their contribute in clarifying some important issues related to drug users mortality. The results of the searches are summarized in the following tables:

NUMBER OF PAPERS COLLECTED

	European countries	Other countries
Longitudinal studies	**24**	**9**
Cross-sectional studies	**14**	**6**
Case-control studies	**1**	**1**
Letters, editorials and reports	**7**	**4**

The complete and chronologically ordered list of the references on mortality among drug users that will be reviewed is included (see APPENDIX).

The items according to which each paper was reviewed are the following:

Longitudinal studies

- Authors and year (Ref. N)
- Study site
- Study population
- Number of subjects
- Follow-up period
- Findings
- Comments

Cross-sectional studies

- Authors and year (Ref. N)
- Study site
- Source of data
- Study period
- Number of deaths
- Findings
- Comments

For longitudinal studies a more detailed review was carried out taking into account methods used to ascertain vital status and causes of death.

Comments

Cross-sectional studies

Twenty-one papers regarding cross-sectional studies have been published between 1970 and 1996. Fifteen studies out of 21 have been carried out in European countries: United Kingdom, Denmark Norway, Austria and Spain.

Very heterogeneous sources of data have been used:

- clinical records
- coroners' registers
- autopsy reports
- police reports
- treatment services records
- toxicological laboratories
- national or local population registers.

The characteristics of the sources of data, criteria and modalities for selecting cases have not always been well specified. The definition of "drug-related" death and more specifically the criteria adopted to distinguish "directly" or "indirectly" drug-related deaths are very heterogeneous among different studies. Furthermore, there are differences as regards the classification of causes of deaths because only in few cases ICD codes have been used.

In a few studies the authors critically pointed out the limits of the sources of data used in describing mortality among drug users.

In most of the studies reviewed, mortality rates have been calculated using different populations at risk as denominator such as number of addicts notified to local or national drug dependence registers, mid-year population resident in a country or in a particular area or, more recently, population of drug users (injectors) estimated with capture-recapture method.

Mortality "rates" obtained by relating the number of "drug-related" deaths to a population at risk different from the population generating the cases, can not be considered valid estimates of mortality of drug users. In this case, in fact, the condition that cases (deaths) must come from the study population it is not satisfied.

Longitudinal studies

All cohort studies on mortality among drug users show death rates higher than expected in a matched general population group, although there is variability across study periods, study population and location.

The following analysis describes the heterogeneity of longitudinal studies reviewed, in terms

of study population and methods used to ascertain vital status and causes of death.

Out of 32 papers reviewed, 20 were published between 1987 and 1996, as shown in the following scheme:

Year of publication	**n°**
1966- 1976	**4**
1977- 1986	**9**
1987- 1996	**20**

As regards the study site 23 studies were carried out in European countries and more specifically: 7 in Great Britain, 10 in Northern Europe (Sweden, Norway, The Netherlands, Denmark and Germany) and 6 in Southern Europe (Spain and Italy).

Longitudinal studies carried out in different countries are heterogeneous in terms of study population, criteria for enrolling subjects, methods used to ascertaining vital status and causes of death as well as methods of analysis.

Mortality rates have been estimated almost exclusively among drug users receiving treatment since identifier information are necessary to ascertain their vital status. In most cohort studies the study population has been enrolled among those who were attending treatment centres as outpatients. Only in few studies (5 out of 32), subjects included in the cohort have been selected among those hospitalized with diagnosis of drug addiction; moreover, in five studies both inpatients and outpatients have been enrolled.

The study population differs among countries with regard to type of drug used and route of administration. In 6 studies out of 32, type of substance abused has not been specified and in 9 studies drugs are generically reported as "narcotics" or " opiates". In most of the studies, use of heroin, alone or associated with other substances, was the first requirements for recluting subjects into the cohorts. In less than half of studies (14 out of 32), the route of administration is specified (mainly by injection or injection and other).

In 31 studies out of 32, methods used for ascertaining vital status have been specified but with some differences with regard to the description of characteristics of data sources. The most frequent sources of information on vital status used in longitudinal studies are local or national population registers, hospital and drug treatment services records and central police registers. In addiction to these sources of data, in a few studies, information on vital status have been obtained through interviews and visits. The latter method for tracing subjects has been used especially in those longitudinal studies that were carried out with not only the purpose of measuring mortality rates but also to detect other addiction outcomes such as abstinence, or continued drug use and

treatment centres attendance.

Ascertainment of causes of deaths has been performed in 29 studies out of 32 using different sources. Information have been obtained from national or local mortality registers where available, hospital and medical examiner reports, coroners' reports and directly from deaths certificates. Only in few studies causes of death have been identified according to the International Classification of Diseases (ICD) and even where official statistics have been used not always ICD codes were specified.

In conclusion, the heterogeneity of methods used to carry out longitudinal studies hampers geographical and temporal comparisons and calls for developing a standardized methodology.

APPENDIX

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REVIEW OF
LONGITUDINAL STUDIES

LONGITUDINAL studies

Authors and year (ref. N)	Vaillant GE , 1966 **(1)**
Study site	USA (Kentucky)
Study population	All male narcotic addicts (28-35 years) coming from NY and admitted to the Lexington Hospital, Kentucky, + a group of unselected male addicts from NY (reference group) "first admitted" to the same hospital in the same period (1.8.53-31.1.53). Participants were classified as abstinent, addicted or possibly addicted, instituzionalized, marginal.
N° of subjects	50 + 100
Follow-up period	From date of enrolment till 1964-65. All participants has been followed for a minimum of 9 years after discharge and at least until the age of 39.
Findings	Among the 132 subjects followed for 12 years, 20 died (12 from the study group and 8 from the reference group). Death rate was three-fold that expected for males of similar age; the death rate for alcoholism complication was very high.
Comments	The study group was biased by containing readmission and was confined between the ages of 28 and 35. The study group contained 18 members of the reference group.

LONGITUDINAL studies

Authors and year (ref. N)	Bewley TH, Ben-Arie O, James P, 1968 **(3)**
Study site	Britain
Study population	All case of heroin addiction first known to the Home Office from 1947 to 1966 (therapeutic and non therapeutic).
N° of subjects	1272 (1237 therapeutic, 35 non therapeutic)
Follow-up period	1954-1964
Findings	69 deaths among non-therapeutics, 16 among therapeutics. Increase in the number of deaths and a decrease in the mean age of death (55% of deaths under 28 years). Mortality rate: 27 per 1000 per annum, 28 times the normal rate in the similar British population and 2 times that of heroin addicts in New York. 1 death for every 37 addicts known to the Home Office. Causes of death: 39% overdose (16 accidental, 7 with suicidal intent), 22% violent death (9 suicides), 22% infectious disease, 17% natural death (directly or indirectly due to drug addiction).
Comments	

LONGITUDINAL studies

Authors and year (ref. N)	Bewley TH, Ben-Arie O, 1968 **(4)**
Study site	London, (United Kingdom).
Study population	Male heroin addicts discharged from Tooting Bec Hospital between 01.10.64 and 31.12.66 (all non therapeutic addicts with 1-2 years of addiction at first admission)
N° of subjects	100
Follow-up period	From enrolment to January 1967-January 1968.
Findings	13 deaths (per 100). Causes of death: 8 overdose, 2 septic pneumonia, 1 suicide, 2 other violent deaths.
Comments	The population is possibly not representative of all the heroin addicts, but is probably representative of the less successful, more ill and more disturbed younger British addicts.

LONGITUDINAL studies

Authors and year (ref. N)	Watterson O, Simpson DD, Sells SB, 1975 **(9)**
Study site	Texas (USA)
Study population	All addicts using opioids daily at time of admission to treatment in the Drug Abuse Reporting Program (DARP) file admitted or continuing a treatment during a 1 year interval over a period of three years.
N° of subjects	I period ('70-'71): 9276, II period ('71-'72):17684, III period ('72-'73): 23529 (not mutually exclusive)
Follow-up period	1.06.70-31.05.71 - 1.06.71-31.05.72 - 1.06.72-31.05.73
Findings	Number of death (Death rates per 1000): I period: 50 (15); II period: 91 (12); III period 134: (13). Death rates for all periods combined: 13 per 1000 (275 deaths), 14 per 1000 for males, 9 per 1000 for females, higher for age >30. Decrease in death rates for people in Methadone Maintenance, low death rates for people in Therapeutic Community. Causes of death: 40% violent, 33% drug related, 23% others, 4% unknown.
Comments	Death rate = number of deaths/total man years at risk per 1000. Time at risk = time in treatment. Understate the death rates for people in the street. Changes in the number of agencies and governmental guidelines.

LONGITUDINAL studies

Authors and year (ref. N)	Thorley A, Oppenheimer E, Stimson GV, 1977 **(10)**
Study site	London (England)
Study population	People attending 13 Drug Dependence Clinics (DDCs) for whom heroin was prescribed as outpatients between March and November 1969
N° of subjects	128
Follow-up period	October 1969 - October 1975.
Findings	12 (9%) were dead; 65 (51%) were attending clinics; 51 (40%) were alive and not attending the clinics. About 33% of the sample were still receiving heroin or prescription, and 23% had received heroin without interruption since 1969.
Comments	Weakness of data from Home Office: they don't know the current status of almost half the sample.

LONGITUDINAL studies

Authors and year (ref. N)	Stimson GV, Oppenheimer E, Torley A, 1977 **(12)**
Study site	London (England)
Study population	see reference n. 10
N° of subjects	128
Follow-up period	Second follow-up between June 1976 and November 1977
Findings	4 people was lost at follow-up. 52 people (41%) had stopped attending the clinics, 6 (5%) were in prison, 55 (43%) were still attending the clinics and 15 had died. 31% reached abstinence from opiates, 48% was still using. Death rate = 16.7 per 1000 per annum. Most common cause of death: respiratory failure due to opiate and barbiturate poisoning.
Comments	Follow-up with a high rate of personal contact. The sample represented the 11% of the total DDCs population in England and Wales. All people dead were drug dependent at the moment of death.

LONGITUDINAL studies

Authors and year (ref. N)	Wiepert GD, Bewley TH, d'Orban PT, 1978 **(13)**
Study site	London (England)
Study population	All patients attending two drug clinics in London, for treatment of opiates dependence, between 1968 and 1975. In 1968 95% depending from heroin, in 1975 98% depending from methadone.
N° of subjects	575
Follow-up period	1968-1975
Findings	52% still in treatment, 11% died, 6% in custody, 3% left the country, 28% left the treatment or lost. Drug abuse was the principal cause of death.
Comments	The rate of death was many times higher than might be expected for the same age group. Those who died had been more inconsistent in attendance, had abused drugs more and had a lower rate of employment.

LONGITUDINAL studies

Authors and year (ref. N)	Concool B, Smith H, Stimmel B, 1979 **(14)**
Study site	New York (USA)
Study population	All heroine addicts admitted for the first time to the Methadone Maintenance and Aftercare Treatment Program (MMATP) between March 1 969 and December 1976 + a control group randomly selected from the entire clinic population.
N° of subjects	1156
Follow-up period	March 1969 - December 1976
Findings	45 death (39 per 1000): 23 (20 per 1000) died while in program, 22 (19 per 1000) died after discharge. Cause of death: 38% violence, 40% medical complications, 9% accidents, 13% overdose. 60 % of deaths was attributable to alcohol. The group of control and the decedents differed by alcoholism, age on dimission, length of addiction, solitary lifestyle. Comparison of death rates between people from MMATP and East Harlem population differed by cause of death when adjusting for age.
Comments	The control group was selected so that the number of controls in a year was proportional to the number of deaths in that year. Methadone was never implicated as a causative factors of death.

LONGITUDINAL studies

Authors and year (ref. N)	Wille R, 1981 **(15)**
Study site	London (United Kingdom).
Study population	see ref N. 10
N° of subjects	128
Follow-up period	1969-1979
Findings	19 (15%) deceased, 49 (38%: 24 persons were being prescribed heroin, the rest methadone only) still attending, 60 (47%) discharged. Death rate= 14.8 per 1000 heroin addicts yearly. Cause of death: 8 respiratory failure due to poisoning, 5 other illness, 2 accidents, 1 suicide, 3 drug addiction
Comments	

LONGITUDINAL studies

Authors and year (ref. N)	Musto DF, Ramos MR, 1981 **(16)**
Study site	New Haven, Connecticut (USA)
Study population	Morphine addicts registered at the New Haven Narcotic Clinic as of May 1920
N° of subjects	91
Follow-up period	29.05.1920 - 1972
Findings	40 death (all white): 51% of the white people, 44% of the total population. The 35 men died 12 years earlier than expected, mean age 57; the 5 women died 18 years earlier than expected, mean age 51. Alcoholism, cyrrosis, suicides, accident and veneral diseases accounted for 26% of death causes, compared to 9% of the population of Connecticut of same age. Tuberculosis accounted for 10%, versus 3%.
Comments	Number of expected death was calculated on the basis of the life expectancy related to the age of the subjects in 1920. No death could be ascribed to overdose of an opiate.

LONGITUDINAL studies

Authors and year (ref. N)	Joe GW, Lehman W, Simpson D, 1982 **(20)**
Study site	USA
Study population	Samples of opiates abusers admitted to community-based treatment programs + a comparison group that didn't receive treatment between 1969 and 1973 (DARP).
N° of subjects	6402, 5340 were located, 78 were excluded for miscellaneous problems, for a total of 5262 .
Follow-up period	From enrolment to 1975-1979
Findings	179 deceased in the first 4 years of follow-up, yielding a death rates of 15.2 per 1000 person-years at risk. When adjusted for age, death rates were found to be 3 to 14 times greater than those in the general US population. Mortality rates were significantly higher for older clients and for heavier alcohol users. Among the variables significantly correlated to survival curves there were: age at DARP admission, pre-DARP alcohol consumption, year of admission to DARP treatment. Causes of death: 28% violence related, 44% drug-related, 17% natural causes, 11% unknown.
Comments	Classification of causes of death were based on death certificates (four categories: violence, drug abuse related, other causes, unknown). Mortality was investigated using life-table analysis (cumulative survival rate for different group). Death rates were computed as the number of deaths/person-years following treatment per 1000. Located cases were used as the population base for computation of death rates.

LONGITUDINAL studies

Authors and year (ref. N)	Benson G, Holmberg MB, 1984 **(23)**
Study site	Denmark (Gothenburg)
Study population	Selected (persons in treatment not older than 25) and unselected drug users from the same area
N° of subjects	UNSELECTED: 1) 4783 pupils in 9th grade school; 2) 2658 military conscript. SELECTED: 3) 213 drug clinic outpatients; 4) 58 psychiatric inpatients diagnosed drug abuse; 5) 231 admitted at drug rehabilitation home; 6) 263 from social welfare files.
Follow-up period	1) 1969-78; 2) 1970-78; 3) 1968-78; 4) 1968-78; 5) 1970-79; 6) 1968-78.
Findings	44 deaths (19 among unselected population, 25 among selected one). A higher mortality was observed n the selected groups; 3) 4.7 times the expected in males; 5) 6.9 times in males, 7.9 times in females; 6) 2.4 times in males. Causes of death: UNSELECTED : MALES: 5 suicides, 6 accidents, 1 alcohol consumption; FEMALES: 5 suicides, 2 accidents. SELECTED: MALES: 12 suicides, 11 accidents, 1 cardiac disease, 1 pyelonepritis.
Comments	The expected age-related mortality was calculated for the selected groups using average from 1969, 1973,1978. Expected mortality for different causes was calculated using data from age 15-24 years, and the period '69-'79 as a basis. Addicts in the unselected groups used cannabis, solvents, LSD, central stimulants. Addicts in the unselected groups were polydrug abusers, including alcohol and a high frequency of central stimulants.

LONGITUDINAL studies

Authors and year (ref. N)	Haastrup S, Jepsen PW, 1984 **(24)**
Study site	Denmark (Copenhagen)
Study population	People in treatment for morphine abuse from Copenhagen Community Hospital and Drug Treatment Service.
N° of subjects	300
Follow-up period	1973-1980 (seven years after the first referral to treatment).
Findings	203 (68%) men and 97 (32%) women. The median age at start of daily intra venous use was 17 years and the median age at first referral to treatment was 21 years. Less than one sixth of the original population could be described at the time of f-up, as an active addicts. 47 deaths. Each year 5-6% of the original population had become drug-free and approx 2% had died. Mortality among the remaining active addicts is rising from year to year, as the active abuser population has strongly declined during the 7-year observation period. Similarly, the percentage of new long-term drug-free cases from the remaining abuser population is rising from year to year. In terms of start of drug abuse the average death rate is 2.3% and the average rehabilitation rate 4.0%. Causes of death: 2 (4%) natural deaths, 10 (21%) accidents, 12 (26%) suicides, 23 (49%) unexplained. Among these, 46% was due to overdoses (intentional or accidental).
Comments	The inclusion criteria were a daily intravenous abuse and a first referral to treatment. The study's most important information was obtained at face to face interviews (prior to the interviews information was gathered from the official sources). The main objective of the study was to describe the progress of the study population during the follow-up period. Because of the lack of any standard rating scale or general rules, a classification scale was constructed on the basis of a combination of drug abuse and occupational status in 1980. The scale had four main classes with 10 subclasses levels.

LONGITUDINAL studies

Authors and year (ref. N)	Joe GW, Simpson D, 1987 **(27**)
Study site	USA
Study population	Black and white males selected from the DARP population (see ref n.20)
N° of subjects	697
Follow-up period	6 years extension of the DARP follow-up (6^{th}- 12^{th} year).
Findings	52 deaths, corresponding to 13.8 per 1000 person-years (lower than the previous: 15.2 per 1000) The average annual risk of death was 1.39%. Causes of death: 28.8% violence-related; 48.1% drug-related, 23.1% others.
Comments	142 (20%) persons lost at follow-up could have been yielded a bias in the mortality rates (small since lost persons didn't differ from the others in the principals characteristics). Mortality rates could be influenced by community and environmental factors.

LONGITUDINAL studies

Authors and year (ref. N)	Tunving K, 1988 **(29)**
Study site	Sweden (Lund)
Study population	Drug addicts admitted to a ward for treatment, offering treatment and detoxification at St. Lars Hospital from 1.07.70 to 1.07.78.
N° of subjects	524 (191 opiate abusers, 197 amphetamine abusers, 136 mixed abuse).
Follow-up period	From the enrolment to 1.07.84
Findings	62 deaths, corresponding to a death rate of 12 per 1000 (more than 3 times higher than expected). The 62 addicts died at an average age of 28 years. Opiate addicts had the higher death rate (24/1000 males, 14/1000 females), while stimulant abusers had the lower 10/1000 in males, no deaths in females). The difference between opiate addicts and amphetamines abusers was significant (P< 0.001). The number of deaths increased during the first 6 years (the period when all in the sample were followed-up), then the death rate decreased a little. Causes of death: 19 suicides, 35 drug-related due to overdoses or intoxications, 8 drug-related due to accidents and violence.
Comments	Man-years were calculated as the exposure to risk of death. Expected deaths were taken from the death risk in the official statistics for the Swedish population in the median year of follow-up (1975).

LONGITUDINAL studies

Authors and year (ref. N)	Haastrup S, Jepsen P W, 1988 **(31)**
Study site	Denmark (Copenhagen)
Study population	Young opioids addicts attending Drug Treatment Service or Mental Hospital in Copenhagen.
N° of subjects	300
Follow-up period	1973-1984
Findings	78 (26%) died. The deaths were distributed evenly over the 11 year period yielding an average mortality of the cohort of 2.4% per year. Among those who died in the period 1980-84, 69% died from drug overdose or other causes linked with intoxication. In 1984, 24% of the cohort were classified in the best outcome class. Sixteen per cent were classified as substance users. The number of active drug addicts declines because they died, not because they achieve abstinence. According to more strict criteria less than 20% would be classified as truly recovered. Another 5-10% achieve some unstable abstinence.
Comments	Criteria of inclusion were daily intravenous abuse of opioids and age less or equal 30. The cohort was followed-up for a personal interview in 1980 and again in 1984. The interviews were completed with data from various registers. In 1984, 90% of the cohort was located. Outcomes were classified on a four-step scale (see ref n. 24) according to current drug status and occupational status. Current drug-free status was not validated by urine screening.

LONGITUDINAL studies

Authors and year (ref. N)	Selwyn PA, Hartel D, Wasserman W, Drucker E, 1989 **(33)**
Study site	USA (New York)
Study population	IDUs in a long-term methadone maintenance treatment program.
N° of subjects	900
Follow-up period	1984-1987
Findings	94 died while in treatment. Increase of proportion dying from 13.3 per 1000 in 1984 to 44.2 per 1000 in 1987 (12.9 per 1000 PY in 1984 to 44 per 1000 person-years in 1987). Causes of death: crude mortality rate for AIDS increased from 3.6 per 1000 in 1984 to 14.7 per 1000 in 1987. Smaller or minimal increase was seen for other causes. Cause-specific death rates (in terms of person-years) among methadone program patients: AIDS rose from 3.5 per 1000 in 1984 to 14.7 per 1000 in 1987; pneumonia, endocarditis and bacterial sepsis together: from 3.5 per1000 in 1984 to 13.5 per 1000 in 1987. Deaths due to alcoholism/cirrhosis and drug overdose remained relatively constant between 1984 and 1987 (3.5 to 5.7/1000 person-years). Death rates from trauma, including homicide, suicide, and vehicular trauma, showed a slight increase during the study period (2.4 to 6.8/1000 person-years).
Comments	Mortality rates were calculated using the midyear population census as the denominator for each year person-time was based on time spent enrolled in the methadone program.

LONGITUDINAL studies

Authors and year (ref. N)	Gronblad L, Ohlund LS, Gunne LM, 1990 **(34)**
Study site	Sweden
Study population	Heroin addicts giving methadone maintenance treatment in comparison to street heroin addicts.
N° of subjects	1) 166 Methadone Treatment patients (MT); 2) 34 voluntary discharged; 3) 53 discharged for violation of program rules; 4) 17 randomized controls; 5) 98 waiting list controls.
Follow-up period	1967-1988. 1) 1967-1979; 2) and 3) from the day of discharging (if a person went back to cohort 1, the second period was added to the first); 4) starting from the day of randomization; 5) starting the day of referral to MT and stopped when deleted from the waiting list.
Findings	96 deaths. High significative differences between treated and controls. 1) **deaths** =16, **death rate**=1.45, O/E per year=8.4; 2) 6, 1.65%, 3.8; 3) 26, 6.91%, 55.3; untreated (cohort 4 and 5) 48, 7.2%, 63,1. Causes of death: majority due to overdoses, mostly by the i.v. route (no overdoses of heroin occurred among those treated with methadone); suicides: 7 in cohort 1), 1 in cohort 2), 3 in cohort 3).
Comments	The 2 control groups didn't significantly differ from each other when their mortality rate was tested according to log-rank test. These 2 cohorts were therefore combined, forming a group of "untreated controls" (this term should not be taken literally, since they all underwent intermittent detoxification and participated in drug-free treatment trials, mostly of short duration.

LONGITUDINAL studies

Authors and year (ref. N)	Engstrom A, Adamsson C, Allebeck P, Rydberg U, 1991 **(36)**
Study site	Sweden (Stockolm County)
Study population	Patients hospitalized with at least 1 diagnosis of drug addiction during 1971-1972.
N° of subjects	1630
Follow-up period	1973-1984
Findings	446 died during follow-up (296 males and 150 females).Overall excess mortality: SMR=5.3. Opiate male users (mostly by i.v. route) were particularly at risk (SMR= 18.3), and also central stimulant users (SMR=9.0). Average yearly deaths=2.3%. Causes of death: mental disorders SMR=43.3 (this group consisted of 52% with an alcohol diagnosis, 19% opiate diagnosis and 29% mixed abuse); 51% died for injury or poisoning (SMR=17.6); 3.4% died for cyrrosis due to alcohol; 69% of the patients had committed suicide.
Comments	Person-years at risk were computed for each calendar year of the follow-up, distributed by sex and age. They used the official death rates for Stockolm County to compare the observed number of death to the expected ones for the total mortality and the death rates of the whole of Sweden for the mortality by cause of death.

LONGITUDINAL studies

Authors and year (ref. N)	Perucci CA, Davoli M, Rapiti E, Abeni DD, Forastiere F, 1991 **(37)**
Study site	Rome (Italy)
Study population	IVDUs attending the 3 largest Public Treatment Centres (PTCs) in Rome.
N° of subjects	4200
Follow-up period	1980-1988
Findings	239 deaths (SMR=10.1). Causes of death: overdoses death rate = 3.38 per 1000 person-years; violence =1.62 per 1000 PY, cyrrosis = 0.88 per 1000 PY; AIDS death rate increased from 0.4 in 1986 to 2.7 per 1000 PY in 1988. The SMR for all causes was higher among females than among males.
Comments	Person -years at risk of dying= from the day of first enrolment to the end of follow-up or to the death. SMR was calculated to compare observed death to mortality of the national population. Expected number of deaths were calculated using sex and age-specific national mortality rates.

LONGITUDINAL studies

Authors and year (ref. N)	Mientjes GH, van Ameijden EJ, van den Hoek AJAR, Coutinho RA, 1992 **(39)**
Study site	Amsterdam (the Netherlands).
Study population	HIV+ (non AIDS) and HIV- IVDUs recruited at 6 low-threshold methadone outposts and at a weekly STD clinic for drug abusers prostitutes
N° of subjects	390 (193 HIV - randomly selected and 197 HIV +)
Follow-up period	1986-1989
Findings	26 (6.6%) died of causes other than AIDS, 17 (8%) were HIV+ and 9 (3.6%) were HIV -. Causes of death: overdoses, accidents and suicides: 10; unknown: 10. The overall incidence rate for non-AIDS mortality was 0.023 per PY (N=390) for HIV - and 0.038 per PY (N=420) for HIV+. RR for HIV+ =1.65 not significant.
Comments	Patients who were HIV-infected at study entry and were diagnosed with AIDS during the study period, were excluded from the study on the date of AIDS diagnosis (to study only non-AIDS mortality). The Relative Risk refers to the number of hospitalizations of HIV+ compared to HIV -.

LONGITUDINAL studies

Authors and year (ref. N)	Perucci CA, Forastiere F, Rapiti E, Davoli M, Abeni DD, 1992 **(40)**
Study site	Rome (Italy)
Study population	see ref. N 37
N° of subjects	4200
Follow-up period	1980-1988
Findings	213 deaths (SMR=10.5). Excess mortality was found in both sex for all causes (SMR=9.6 males, 20.1 females). Overdose, violence, cyrrosis, cardiovascular disease and AIDS play a preminent role. 11639 persons aged 15-34 years resulted to be at risk of dying from overdose in Rome, corresponding to an average annual prevalence of 22.3 per 1000 male and 5.17 per 1000 female. The deaths attributable to injecting drug use was 16% in male and 9% in females. The cause-specific attributable proportions were 66% for endocarditis and 37% for cirrhosis in males, and 36% for endocarditis and pneumonia in females.
Comments	To calculate the proportion of all deaths attributable to injecting drug use in the age group 15-34, the formula of the Population Attributable Risk has been used. The prevalence of the risk factor (i.e. the proportion of IVDUs) in the general population was estimated using the "multiplier formula" and "capture-recapture" methods.

LONGITUDINAL studies

Authors and year (ref. N)	Eskild A, Magnus P, Samuelsen SO, Sohlberg C, Kittelsen P, 1993 **(41)**
Study site	Norway (Oslo)
Study population	HIV+ and HIV- IVDU (who had ever injected drugs after 1979, 60% heroin, 10% amphetamine, 30% both) recruited by the Department of AIDS prevention, for HIV testing.
N° of subjects	1009 (180 HIV+ AND 829 HIV -)
Follow-up period	From the date of the first test until death or the end of follow-up (01.01.91)
Findings	87 deaths. The estimated probability of survival after 3 years follow-up was totally 0.92 (0.87 HIV + and 0.93 HIV -; difference statistically significant). The RR of death of the total cohort was 31. The highest RR of dying was seen among HIV + and HIV - females in the youngest age group. The estimated mortality was generally higher than for the general population. Causes of death: drug overdose 58 (67%); AIDS: 4; homicides or accidents: 4; other than AIDS: 2. Adjusted RR of dying from any cause for HIV +: 2.1. The other variables which were significantly associated with progression to death were >= 30 years of age and >= 5 years of IV drug use prior to study entry. The crude RR of overdose death for HIV positives compared to HIV negatives was 1.7 and the adjusted RR was 1.4 (not significant).
Comments	An IVDUs was defined as a person who had ever injected drugs after 1979. Mortality rates=number of deaths/ PY during the period for each group of variables (age, HIV status, gender). RR (compared to the general population)= mortality rates in each group / mortality rates in the general population. Variables used for the adjusted analysis: gender, age at study entry, duration of IVD, year of study entry.

LONGITUDINAL studies

Authors and year (ref. N)	Oppenheimer E, Tobutt C, Taylor C, Andrew T, 1994 **(49)**
Study site	London (England)
Study population	Heroin injectors attending DDCs in London in 1969 (see ref N 10)
N° of subjects	128
Follow-up period	1969-1991
Findings	43 (38% of those traced) died. Cause of deaths : 28 (68%) primarily associated with drug abuse; in particular 18 overdose and 10 other drug-related. 13 (32%) not primarily associated with drug abuse; in particular 2 suicides, 3 accidents 7 natural and 1 homicide. Mortality rates=1.83%. Excess mortality ratio=11.9. The highest mortality rate was in the period 1983-1988 (2.64%), while the lowest was in the two period 1971-76 and 1977-82 (1.55%).
Comments	Excess mortality rate = observed number / number expected to die in an age and sex-matched sample of the general population in a similar period.

LONGITUDINAL studies

Authors and year (ref. N)	Zaccarelli M, Gattari P, Rezza G, Conti S, Spizzichino L, Vlahov D, Ippolito G, Lelli V, Valenzi C, 1994 **(50)**
Study site	Rome (Italy)
Study population	IDUs attending 2 Drug Centres in Rome who underwent HIV testing between 1985 and 1991.
N° of subjects	2431 IDUs: 770 (31.7%) were HIV -seropositive at enrolment; 1661 (68.3%) were HIV -seronegative, 82 of whom seroconverted during the study period
Follow-up period	1985-1991
Findings	181 deaths: 89 due to AIDS, 43 to overdose and 49 to other causes. Total mortality rate increased over the study period from 1 death (0.8%) in 1985 to 42 (3.6%) in 1991. The rate of death due to AIDS increased from 0.4 to 1.8% and death due to overdose from 0 to 0.5% in the same period. Among men, the mortality rate was significantly higher for HIV+ than HIV- IDUs (Estimated Relative Risk 5.1) The difference remained statistically significant (ERR 1.6), even after excluding deaths from AIDS. Among women, the excess of mortality was also statistically significant both including and excluding AIDS deaths (ERR 7.8 and ERR 4.7 respectively). The excess of mortality among the IDUs population was the following : SMR =34.9 in males and 24.2 in females. HIV+ IDUs showed an excess for death due to overdose and to cardiovascular disease. There was no difference in the rate of deaths due to pneumonia by HIV serostatus. Survival analysis showed a proportion of survivors =0.975 for HIV-, 0.927 for seroconverters and 0.825 for HIV+ (significant difference). In the multivariate analysis HIV+ had a 4.5 greater risk of dying than HIV - IDUs, and the risk and a 6% increase for every year of age.
Comments	The covariates used in the multivariate analysis were HIV status, age and sex. Limitations with respect to selection of study participants: IDUs were recruited from drug-treatment centres only (duration of infection is unknown); age was missing for nearly 20% of the participants (caution in interpreting results concerning the effects of age on mortality); no information on behaviour and drug-treatment history was available; with regard to the SMR, these were calculated on a selected population of IDU undergoing HIV serological testing in two drug-treatment centres.

LONGITUDINAL studies

Authors and year (ref. N)	Robertson JR, Ronald PJM, Raab GM, Ross AJ, Parpia T, 1994 **(51)**
Study site	Edinburgh (Scotland)
Study population	IVDUs participating to the Edinburgh drug addiction study, recruited following a consultation with a medical doctor of the Muirhouse Medical Group between 1982 and 1985.
N° of subjects	203
Follow-up period	Follow-up conducted between January 1990 and June 1993.
Findings	From the start of follow-up in 1990, 163 (91%) of the 180 survivors (23 subjects died before 1990) were traced, of whom 116 (71%) were interviewed. Dramatic changes had occurred in drug taking, with a move away from injecting towards oral drug use. A few patients continued to inject. 90 (78%) of those interviewed had been in prison, of whom 37 (41%) had injected drugs while in prison. There were 40 deaths (from 1983 to the end of 1992): 15 were attributed to overdose and 16 were AIDS related deaths, 10 of which occurred in 1991.
Comments	Mortality rate and Person-years at risk were not calculated.

LONGITUDINAL studies

Authors and year (ref. N)	Galli M, Mussicco M, 1994 **(53)**
Study site	Milan (Italy)
Study population	IVDUs voluntarily attending 4 public drug dependence treatment centres in Milan Metropolitan Area (MMA) between 01.01.80 and and 31.12. 88, that could be traced in the registry offices of the municipalities of MMA since 1981.
N° of subjects	2432
Follow-up period	Follow-up was closed on June 1991.
Findings	At the end of follow-up the cohort accounted for 16415 PY of observation. 413 deaths were registered (16%). The overall mortality rate was equal to 25.2 per 1000 PY. The main causes of death were: 151 overdose (36.6%), death rate=9.2 per 1000 PY; 144 AIDS (34.9%), death rate=8.8 per 1000 PY; 11 infectious disease (2.7%), death rate=0.7 per 1000 PY. Mortality remained under 16 per 1000 PY from1981 to 1986, then increased rapidly to 63.8 per 1000 PY in the first half of 1991. AIDS and overdose accounted for most of this increase, with AIDS becoming the leading cause of death from 1989. Compared to the Milan overall mortality rate, the age, calendar year and sex-adjusted SMR of the IVDUs cohort was=20.5. HIV+ individuals showed a significantly higher overall mortality (48.0 per 1000 PY) than those with unknown serological status (19.9 per 1000 PY), due almost entirely to AIDS. HIV-1 infection does not appear to affect the mortality for causes other than AIDS and infectious diseases.
Comments	Expected deaths=specific mortality rates for the general population of Milan of the same age and sex. Limitation of the study: some individuals with unknown HIV-status were actually infected, probably leading to an underestimate of HIV prevalence and a lower difference between the two groups. Selection bias, since the cohort is hospital-based: patients who refer to the hospital may have more advanced disease.

LONGITUDINAL studies

Authors and year (ref. N)	Goedert JJ, Pizza G, Gritti F, Costigliola P, Boschini A, Bini A, Lazzari C, Palareti A, 1995 **(59)**
Study site	Italy (Bologna and province and S. Patrignano Therapeutic Community)
Study population	Drug users who was enrolled at least once on a treatment program between 1.1.80 and 2.7.90 + drug users seen at the medical service of the regional jail and at 2 hospitals in Bologna (infectious diseases clinics and wards)
N° of subjects	4962
Follow-up period	January 1980 - November 1990
Findings	332 deaths. Mortality rate=1.57 per 100 PY, was 18-fold higher than that reported for adults in the city of Bologna. Mortality rate was highest for HIV+ (2.6 per 100 PY) compared to untested (1.34%) and HIV - (0.28%). The highest mortality rate by HIV status, sex and age-group was found in HIV+ men aged 30-63, the lowest in HIV - women. Causes of death: 51 unknown, AIDS :150, overdose: 64, cyrrhosis: 25, other bacterial infection: 14. Both AIDS and non-AIDS unadjusted mortality-rates increased with age. Mortality due to bacterial pneumonia, tuberculosis, other bacterial infections, and hepatic diseases, but not non-AIDS cancers, is increased with HIV-1 infection.
Comments	Person-Years at risk were calculated from the earliest enrolment date (1.1.80) to date of death or latest available date from any source if not known to be dead. Mortality rates for age, sex and HIV status strata were estimated by the Kaplan Meier method.

LONGITUDINAL studies

Authors and year (ref. N)	Fugelstad A, Rajs J, Bottiger M, Gerhardsson de Verdier M, 1995 **(61)**
Study site	Stockolm (Sweden)
Study population	All known HIV+ IDUs in the Stockolm area during 1986-90 reported to the National Epidemiological Centre attending MMTP or not.
N° of subjects	472 (135 participated in Methadone Maintenance Programme)
Follow-up period	1986-1990
Findings	69 deaths. A majority, 52 subjects, died as the result of violence or poisoning (41 deaths were related to injection of heroin, 9 were attributed to suicide). Seventeen people died from somatic consequences of drug and alcohol abuse (among these 9 died from AIDS). The incidence rate for all causes of death was 3.3/100 PY for IDUs in the MMTP, 3.7/100 PY for those never in the programme and 11.1/100 PY for those discharged from the programme. The latter had a RR of dying compared to the IDUs never included in the programme =3.0. The incidence rate for cause of death related to violence or poisoning was 0.8/100 PY for IDU s in the MMTP, 3.1/100 PY for those never in the programme and 8.9/100 PY for those discharged. The RR of the IDUs in the MMTP and of the discharged were respectively 0.3 and 2.9.
Comments	Person-Years were calculated for different age group, knowing the date of birth and the date of first positive test. The HIV+ IDUs population in Stockholm is well represented. The groups of IDUs Methadone Treatment and those discharged are small, so that RR Confidence Intervals are wide. The decreased risk observed could be biased by the exclusion from the programme of the cases with a higher mortality rate.

LONGITUDINAL studies

Authors and year (ref. N)	Mc Anulty JM, Tesselaar H, Fleming DW, 1995 **(62)**
Study site	USA (Portland,Oregon)
Study population	IDUs not currently (within last 30 days) enrolled in any treatment programme, recruited through outreach workers and public clinics between April 1989 and March 1991.
N° of subjects	1769
Follow-up period	April 1989 - December 1991
Findings	33 deaths, resulting in a crude death rate of 1048 per 100,000 PY. The age-adjusted RR of death was =8.3, compared to the Oregon population. Causes of death: 13 overdoses (39%), 5 trauma (15%), 4 infections (12%)
Comments	Impossible to identify predictive factors of premature death, because of the small number of deaths. Difficulty to find out-of-state deaths (only matching with death certificates): the mortality rate for the cohort of out-of-treatment injection drug users is at least as high as that for injection drug users enrolled in treatment, and may be an underestimate.

LONGITUDINAL studies

Authors and year (ref. N)	Friedman LN, Williams MT, Singh TP, Friedman TR, 1996 **(63)**
Study site	USA (New York City)
Study population	Welfare clients (18-64 years) who were given an examination to assess employability on 10 preselected days in the third quarters of 1984, with a history of alcoholism (average daily consumption of 2 oz for at least 1 month) and/or drug abuse (unprescribed injection of any drug at any time or daily use of any orally or nasally narcotic for at least 1 month)
N° of subjects	858
Follow-up period	1984-1992
Findings	183 deaths (21.3%), with a death rate of 2842 per 100,000 PY, 5.2 times the age-matched general population. The main causes of death were: 66 AIDS (36.1%), 11 tuberculosis (6.0%), 18 infectious disease (9.8%), 16 cirrhosis (8.7%), 8 overdose (4.4%) , 7 cardiac diseases(3.8%). Abusers of both drugs and alcohol were at significantly higher risk of dying (adjusted RR: 1.7).
Comments	The study is part of a cross-sectional study on incidence of tuberculosis, from which 100 subjects with unknown date of birth, 10 with active tuberculosis and 2 with an AIDS diagnosis before the beginning of the study have been excluded.

LONGITUDINAL studies

Authors and year (ref. N)	van Haastrecht HJA, van Ameijden EJC, van den Hoek JAR, Mientjes GHC, Bax JS, Coutinho RA, 1996 **(64)**
Study site	Amsterdam (The Netherlands)
Study population	Injection and non injection drug users recruited through "low-threshold" methadone program and through a sexually transmitted disease clinic for drug-using prostitutes, from December 1985 until July 1, 1992 (with restriction to participants with Dutch nationality)
N° of subjects	632
Follow-up period	Follow-up was closed on 01.02.1993.
Findings	At study entry, 489 (77%) participants reported ever having injected drugs, while 20 more reported at a repeat visit that they had initiated drug injection. At entry, 139 (28%) injection drug users were HIV+, while another 32 seroconverted in the course of repeat visits. A total of '72 deaths among IDUs were recorded (two deaths occurred among persons who started drug injection in the course of repeat visits) and 5 among non IDUs. Causes of death in IDUs: 16 overdose (7.2 per 1000 PY), 12 AIDS (5.4 per 1000 PY), 10 suicide (4.5 per 1000 PY), 8 infections (3.6 per 1000 PY). The crude overall mortality rates was 32.3/1000 PY in IDUs and 8.8/1000 PY in non IDUs, giving a rate ratio of 3.65. Among IDUs, HIV+ had a 3.6 times higher mortality risk. In multivariate analyses, limited to injection drug users, a positive HIV serostatus, age above 40 years, and using benzodiazepines several times daily were significantly associated with an elevate risk of death both for death from all causes and for death preceding AIDS diagnosis. Only 38% of HIV-infected injection drug users who died were diagnosed with AIDS.
Comments	Vital status was ascertained for 593 (94%) subjects. IDUs were defined as those who had ever injected drugs. Those who started injecting after the enrolment in the study changed their status from non injecting to injecting. A bias could have been occurred in the follow-up, because some people couldn't be censored because of having moved out of Amsterdam (sometimes, in fact, drug users who became ill tend to move).

LONGITUDINAL studies

Authors and year (ref. N)	Ortì RM, Domingo-Salvany A, Munoz A, Macfarlane D, Suelves JM, Anto JM, 1996 **(65)**
Study site	Catalonia (Spain)
Study population	Opiates addicts gathered from data bases regarding emergency rooms (ER) and treatment centres (TC), resident in Catalonia and aged 15-44, between 01.01.85 and 31.12.91. Record linkage was performed to obtain a cohort with unique individual data. Addicts were categorised in 3 groups according to the source of entry with which they were registered (ER, TC or both).
N° of subjects	15711
Follow-up period	Follow-up started at the age of 15 or at the age of first admission if age was greater than 15, and finished at the age of 45, age on 31.12.91, age of death
Findings	Men were mostly recruited through TC. Fatality rates were highest among patients with ER as the only source of entry, women had lower overall fatality rates and were younger than men. Mortality rates increased over the period from 13.8 to 34.8 per 1000 PY (the increase was statistically significant in the periods 1987-88 and 1988-89). In the multivariate analysis (adjusted for age, gender, source of entry and length of drug use) the risk increased significantly in men and for longer length of use. The principal causes of death were overdose or dependence (10.9/1000 PY) , AIDS (10.8/1000 PY) and violence (3.7/1000 PY). All these causes showed increasing rates during the period, but AIDS had a greater slope, being the most important cause since 1989.
Comments	Person-years were calculated for each category defined by gender, source of entry and calendar year. People not detected as dead in the Catalonia Mortality Registry (CMR) were considered alive at the end of the study period. Mortality in the CMR was coded using the ICD, IX Revision

LONGITUDINAL studies

Ref. N	Setting	Ascertainment of vital status	Ascertainment of causes of death
1	Inpatients	YES: F-up project of the US Public Health Service, current arrest records, Social Security Records	YES: all confirmed by death certificate most of all confirmed by autopsy
3	Outpatients	???	YES: hospital notes, death certificates, coroners
4	Inpatients	YES: Dangerous Drug Branch of the Home Office	NO
9	Outpatients	NO	YES: Narcotic Addict Rehabilitation Branch of the National Institute of Mental Health the National Institute of Mental Health
10	Outpatients	YES: DDCs records	NO
12	Outpatients	YES: DDCs registers, NHS central registers, hospitals, voluntary agencies, relatives, prisons, Mental Health Index, hostels	YES: Clinical notes, death certificates, coroners' inquest
13	Outpatients	YES: clinic records, Home Office, coroners' report hospital and physician records	NO
14	Outpatients	YES	YES: Food and Drug Administration
15	Outpatients	YES: Home Office and DDCs	NO

Ref. N	Setting	Ascertainment of vital status	Ascertainment of causes of death
16	Inpatients??	YES: Clinic records, city directories, death notices, ecological zoning maps	YES: death certificates, Connecticut vital statistics
20	Methadone maintenance pr., therapeutic communities, outpatients drug-free treatm., outpatients detoxification pr., intake only	YES: questionnaires, DARP treatment	YES: death certificates, medical examiner reports
23	Outpatient care, inpatient psychiatric care, drug rehabilitation home social welfare files students, military conscripts	YES: National Central Bureau of Statistics	YES: National Central Bureau of Statistics
24	Inpatients-outpatients	YES: interviews and official sources: Central Population Registry, Institute for Psychiatric Demography, Central Police Registry, Drug Treatment Services	YES
27	see Ref N. 20	see Ref N. 20	see Ref N. 20
29	Inpatients	YES: Central and parish registers	YES: Central Mortality Register (ICD-8)
31	Outpatients- Inpatients	YES: Interview, Central Population Registry and Central Policy Registry	YES: Death certificates
33	Outpatients	YES: registries recording AIDS diagnoses and death among patients of the program, hospitalizations	YES: hospital records, death certificates, medical examiner reports

Ref. N	Setting	Ascertainment of vital status	Ascertainment of causes of death
34	Outpatients	YES: National Mortality Register	YES: autopsy reports
36	Inpatient (care register)	YES: National Cause Death Register	YES: National Cause Death Register
37	Outpatients	YES: Registry Office of the last municipality of residence	YES: National Mortality files (ICD IX), Registry Office of the municipality of death
39	Outpatients	YES: MM programs, drug aids institutions, Registries of birth, death and Marriage (BDM)	YES: hospital records, BDM registries, post-mortem examination
40	Outpatients	see Ref N. 37	see Ref N. 37
41	Outpatients	YES: National AIDS registry, Central Bureau of Statistics, National Cause of Death Registry	YES: National Cause of Death Registry (ICD-9)
49	Outpatients	YES: interview, clinical notes, Office of Population Census and Surveys, National Health Service Home Office Index	YES: death certificates from Home Office Index
50	Outpatients	YES: Register office of the municipality of last residence	YES: death certificates + clinical records (ICD-9)
51	Outpatients	YES: General Register Office	YES: General Register Office

Ref. N	Setting	Ascertainment of vital status	Ascertainment of causes of death
53	Outpatients	YES: register office of the municipality of residence	YES: death certificates, clinical records of the drug centres, (and, when available, hospital charts and autopsy reports)
59	Outpatients-Inpatients	YES: local and national AIDS registries, vital statistics registries, compulsory registration list of the municipality	YES: death certificates (ICD-9)
61	Outpatients	YES: Methadone Maintenance Programme (MMTP) in Stockholm and Uppsala, Department of Forensic Medicine, hospital records	YES: autopsy reports, forensic chemical analysis, police reports, hospital records
62	Outpatients	YES: ???	YES: death certificates
63	Outpatients	YES: NYC tuberculosis registry, Vital records registry, AIDS registry	YES: Bureau of Vital records and death certificates
64	Outpatients	YES: visit + interview or Register of population in the town of residence	YES: hospital records, coroners' office
65	Outpatients-Inpatients	YES: Catalonia Mortality Registry	YES: Catalonia Mortality Registry (ICD-9)

REVIEW OF
CROSS-SECTIONAL STUDIES

CROSS-SECTIONAL studies

Authors and year (ref. N)	Gardner R, 1970 **(5)**
Study site	London
Source of data	Home Office and Coroners' Registers (from the four Inner London Courts and all inquest cases in two of them)
Study period	January 1965 to December 1968; incomplete data available for 1969 (from Home Office)
Number of deaths	112 + 58 in 1969
Findings	All people "non-therapeutic" opioid users. 21% not previously known to the Home Office (1965-1968) (mean age lesser than that of addicts already registered). In the period 1965-1968: 72% of deaths from drug misuse - i.e. overdosage, infection or treatment - excluding suicidal overdosage. 79% in 1969. 59 non-suicidal overdose in 1965-1968 and 38 in 1969. Most misused drugs: heroin and then barbiturates. Significant increase of deaths from methadone overdosage (suicidal or not): from 10% in 1965-67 to 50% in 1968. In the 1965-1968 series 55 died shortly after a period of opioid abstinence
Comments	Some criticism as regard the use of Home Office List to calculate mortality rates among heroin users (the addicts listed in the Home Office Index are only a subgroups).

CROSS-SECTIONAL studies

Authors and year (ref. N)	Sapira J D, Ball J C, Penn H, 1970 **(6)**
Study site	Lexington, Kentucky (USA)
Source of data	Lexington Hospital (clinical records, autopsy reports)
Study period	From May 29, 1935 to December 31, 1966
Number of deaths	385 (90% males) among narcotics addicts hospitalized
Findings	25 non-natural deaths defined as violent (suicide, homicide and traumatic accident) or drug related. Causes of deaths: 33.2% infectious; 22.3% circulatory diseases; 17.7% neoplastic process; 11.4% metabolic deaths. 9 deaths directly related to drug abuse(2.3%) and 16 (4.1%) violent deaths.
Comments	Analysis of mortality not only from acute causes but also from chronic diseases. The study population includes addicts from throughout the United States; no selection by race, sex or ethnic group as admissions to the hospital over the 31 years considered have reflected the demographic changes among addicts in general.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Cherubin C, McCusker J, Baden M, Kavaler F, Amsel Z, 1972 **(7)**
Study site	New York (USA)
Source of data	Narcotic Register of the New York Health Department and Office of the Chief Medical Examiner
Study period	1950 - 1970 and 1967
Number of deaths	From 50 in 1950 to 1200 in 1970; in the second part of the study 591 deaths in 1967 were considered
Findings	Increase of the annual number of deaths from use of narcotics (from 1950 to 1970). The marked increase from 1967 to 1970 was paralleled by a large increase in reports of addicts to the Narcotic Register. Mortality rates: 1.28% in 1964, fairly constant from 1965 to 1968 (about 0.7%). 78% of deaths in 1967 due to "narcotism" (as reported in death certificate). In 90% of these deaths evidence of recent intravenous injection. "Narcotism" deaths strictly resemble for demographic characteristics the Register population and this would suggest that there is no especially high risk group among addicts for this cause of death.
Comments	Definition of "addict" specified: "person recognized as current illicit users by the source of data used". Description of the characteristics of sources of data. Denominator of mortality rates: n° of addicts known to the Narcotic Register at the middle of each year; numerator: addicts died already known to the Register.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Ghodse A H, Sheehan M, Stevens B, Taylor C, Edwards G, 1978 **(11)**
Study site	Greater London
Source of data	Eight Coroners' Courts
Study period	From January 1970 to December 1974
Number of deaths	134 + 14 (10% random sample) addicts whose cause of death not apparently directly related to their addiction. Estimated addicts died during the five years: 274+/- 75 (95% C I for Poisson sampling)
Findings	78% of the main sample were males; 75% under 30 and 41% unknown to the Home Office. 53% of deaths attributable to barbiturates overdose (in 62% of these cases addicts were known to the H.O). 15% deaths from opiates other than methadone.
Comments	Case definition: "death due to addiction" notified to coroners (regardless of the cause of death recorded and category of drugs). Description of characteristics and limits of the Home Office Index. Some criticism as regard the possibility of Home Office to reflect the prevalence of all serious form of addiction.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Zimney E L, Luke J L, 1981 **(17)**
Study site	District of Columbia (USA)
Source of data	District of Columbia Medical Examiner's Office; Regional Laboratory of the Drug Enforcement Administration (for the analysis on street heroin samples)
Study period	July 1971 - December 1979
Number of deaths	287 deaths directly related to narcotic abuse
Findings	193 deaths (67.2%) due to heroin, 64 (22.3%) to methadone, 21 (7.3%) to heroin+methadone. Mean age 26.8 years; 83% males. Marked geographic clustering of deaths within the principal narcotic usage area of the city. 142 (49%) known as chronic users (opiate tolerance at the time of death). Evidence of conjoint use of alcohol in 37% of the deaths from heroin. During the study period variations in number of deaths and in type of drug identified. Free morphine was identified more often in the blood of victims dying rapidly than in the blood of those with longer post-injection survival. Significant correlation between number of heroin-related fatalities and the purity of heroin available
Comments	Narcotic related deaths separated in two categories depending on the circumstances of death. The study group consists of deaths directly related to the use of narcotic drugs (excluding fatalities from medical complications of narcotic usage and unnatural causes in narcotic users).

CROSS-SECTIONAL studies

Authors and year (ref. N)	Kringsholm B, Voigt J, dalgaard J B, Simonsen J, 1981 **(18)**
Study site	Denmark
Source of data	Three Danish University Institutes of Forensic Medicine (police reports, death certificates, autopsy report and hospital records)
Study period	1978 - 1979
Number of deaths	215 (94 in 1978 and 121 in 1979)
Findings	79% males; mean age in both men and females 26 years, 41% unemployed. 74 heroin users. In most cases (112 -> 52%) a mixed abuse was present (stated as "abuse of hard narcotics" or "any drug available"), the predominant drug being heroin. In 62% of all cases the manner of death classified as an accident. 58% in treatment just before death.
Comments	Cases classified on the basis of the cause of death: 1) poisoning by one or more drugs or complications to this; 2) narcomania as a contributory factor. No differences between the two groups (for sex, age and residence distribution as well as anamnestic information)

CROSS-SECTIONAL studies

Authors and year (ref. N)	Harvey J G, 1981 **(19)**
Study site	London (four Inner London boroughs)
Source of data	Coroner's inquest data
Study period	1979 - 1971
Number of deaths	175
Findings	The number of male addict deaths was almost three times that of females. 88% of addicts who died were under the age of 35 years and about 50% were not known to the Home Office. 80% of deaths associated with the effects of drugs either directly (overdose 72%) or indirectly. Barbiturates involved in 59% of all cases of overdose, strong analgesics in about 42%. Deaths indirectly caused by drugs (septicaemia, endocarditis and hepatitis) were 4.2% of all those attributed to drugs.
Comments	Included all unnatural and violent deaths where a person was reported to be an addict or dependent on drugs or other substances. Difficulties in using coroners' inquest data in identifying deaths of addicts are explained.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Samkoff J S, Baker S P, 1982 **(21)**
Study site	United States
Source of data	National Centre for Health Statistics (NCHS)
Study period	1970 - 1978
Number of deaths	67851 deaths ascribed to poisoning by drugs and medicaments. 22826 (34%) classified as unintentional (E-850-859) drug poisonings were further analysed.
Findings	34% unintentional (E 850-859); 41% suicide (E950.0-3); 12% undetermined intent (E980.0-3); 13% drug dependence (304). Results of analysis of mortality for unintentional drug poisonings: mortality rates per million population declined between 1975 and 1978 from 14.7 to 8.8 (40%). 73% of this drop attributable to a reduction in deaths coded to opiates (E853.0) and intravenous narcotism (E854.8). Death rate for men was twice the rate for females. Mortality rates were especially higher for ages 20-29, for males and for non-white. Time trends in mortality from opiate poisoning appear to coincide with variations in the amount of heroin smuggled into the country.
Comments	ICD VIII codes on the basis of deaths certificates information obtained from the states. Problems in analysis of vital statistics data for drug related deaths. Whether a heroin overdose is coded as "accidental" ,"undetermined" or "natural death due to drug dependence", depends on the information available to the medical examiner or coroner and the data recorded on death certificate. The authors point out that deaths coded as "drug deaths undetermined", and "drug dependence" peak in 1971 and 1975, showing the same pattern as deaths attributed to unintentional poisoning.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Spear H B, 1982 **(22)**
Study site	United Kingdom
Source of data	a) Home Office; b) H M Coroners; c) Office of Population Censuses (for England and Wales); d) Registral-General (for Scotland)
Study period	1978 - 1980
Number of deaths	622 (1978: 192; 1979: 203; 1980: 227)
Findings	622 deaths associated with a "controlled drug " use (drugs included in the Schedule to the Misuse of Drugs Regulations, 1973). 228 (36.6%) deaths previously unknown to the Home Office. Overall rise (18%) in the total number of deaths in the three years period mainly due to increase in the group previously unknown to the Home Office. Overdose of various drugs main cause of death in the "known" addict group (58%). Much higher proportion of overdoses in the "unknown" group. Higher involvement of opioids among the "unknown" addicts deaths. Higher proportion of overdoses from barbiturates in the group of addicts "known" to the Home Office.
Comments	The characteristics of the sources used and their limits in describing addicts mortality are specified. Differences between the two group studied due to the methods used to identify the "cases".

CROSS-SECTIONAL studies

Authors and year (ref. N)	Ghodse G, Sheehan M, Taylor C, Edwards G, 1985 **(26)**
Study site	United Kingdom
Source of data	Home Office
Study period	1967 - 1981
Number of deaths	1499 (1273 - 85%- among "non-therapeutic" addicts)
Findings	Ratio men:women 3.5:1. Over half of "therapeutic addicts" aged 50 or more. 60% of "non-therapeutic" addicts aged 20-29. Drugs caused or were implicated in the deaths of 939 (74%) of "non-therapeutic" addicts, but the drug was identified in only 745 deaths: 7% heroin; 30.5% barbiturates (in the early and mid-1970s); 15% other opiates (10.6% during the last five years) and 11% methadone. Crude mortality rates from 23.5/1000/year for the period 1968-1970 to 18.4/1000/year for the period 1978-1980
Comments	Crude mortalities calculated by relating the number of deaths of addicts notified to the Home Office to the total years of notification (year at risk). Information only refer to addicts known to the Home Office (it is not necessarily applicable to others) and this limit is specified. All notified addicts who died from 1967 to 1981 were included whatever the cause of their death. Discrepancy between the number of deaths of addicts shown by the search of the index of deaths and the number reported in official Home Office statistics

CROSS-SECTIONAL studies

Authors and year (ref. N)	Kringsholm B, 1989 **(30)**
Study site	Denmark
Source of data	Three University Institutes of Forensic Medicine
Study period	1968 - 1986
Number of deaths	1618
Findings	Deaths classified in two groups according to the cause of death: a) poisoning by drugs or complications due to this (82%); b) drug abuse as contributory factor to this. No differences between the two groups regarding demographic data and anamnestic information (combined for the analysis). Number of deaths increases until 1980 (from 5 to 163). Males:females ratio 1:4 in each year. Average age from22/23 years in the early 1970s to 31 years in 1986. Morphine abused in the whole period. Amphetamines abused in the first years and again in 1986. The percentage of deaths among addicts with an abuse more than 10 years gradually increases throughout the period. In the group a) morphine/heroin predominant drug of poisoning (30-50%). Few cases of cocaine poisoning.
Comments	Causes of death classified on the basis of information from: police reports, death certificates, autopsy reports and hospital records if any. No ICD coded specified. Medico-legal autopsy performed in 97% of cases and toxicological analysis in 94% of deaths in the group a).

CROSS-SECTIONAL studies

Authors and year (ref. N)	Klatt E C, Mills N Z, Noguchi T T, 1990 **(35)**
Study site	County of Los Angeles
Source of data	Files of the Autopsy Department of the Los Angeles County-University of South California Medical Centre
Study period	1981 - June 1989
Number of deaths	274 deaths with autopsy evidence of intravenous drug use (patients admitted to a large, acute-care public hospital)
Findings	Mean age 39 years; 214 (78%) males. 127 (46%) deaths unrelated to intravenous drug abuse. The commonest diseases in this group: alcoholism (415), cardiovascular diseases (17%), infections (15%), malignant neoplasm (14%) and accidents (9%). In 147 patients (54%), death was related to intravenous drug abuse, the causes included AIDS (49%), infective endocarditis (19%), overdose syndromes (14%).
Comments	Findings markedly different from reports of deaths in non-hospitalized intravenous drug abusers (including deaths reported to the medical examiner, persons registered as addicts by governmental agencies and military personnel). Different impact upon mortality statistics according to the different kind of study population. Persons hospitalized with a history of intravenous drug abuse die from other causes than overdose (AIDS and chronic alcoholism). Necessity to detect "hidden" intravenous drug deaths to provide more accurate statistical information

CROSS-SECTIONAL studies

Authors and year (ref. N)	Frischer M, Bloor M, Goldberg D, Clark J, Green S, McKeganey N, 1993 **(44)**
Study site	Glasgow
Source of data	Three independent agencies: 1) Procurator Fiscal's Office; 2) General Register Office; 3) Scottish HIV-test Register
Study period	1989
Number of deaths	51 individuals (corresponding to 81 deaths recorded by the three different sources) - **Estimated** population of drug injectors: 9424
Findings	Mortality rate 0.545 in the estimated population (rate for females: 0.85%; for males: 0.42%). Over 90% of deaths attributed to overdose or suicide. 19% HIV+, AIDS caused only 1 death. Mortality rates among HIV+ injectors significantly higher than among HIV- injectors. Male and female injectors respectively 1.5 and 4 times more likely to die than general population of the same sex and age.
Comments	Mortality rates calculated using as denominator the estimated population of drug injectors. The observed mortality rate was lower than in previous studies where the denominators use to calculate rates had an element of underenumeration. The authors point out that ICD currently used to classify drug-related deaths are not precise to discriminate codes injectors from non-injectors. Moreover each drug involved in deaths from overdose should have a separate code

CROSS-SECTIONAL studies

Authors and year (ref. N)	Wysowski D K, Schober S E, Wise R P, Kopstein A, 1993 **(47)**
Study site	United States
Source of data	National Centre for Health Statistics
Study period	1979 - 1988
Number of deaths	Deaths attributed to misuse of psychoactive drugs classified as: a) drug-induced (drugs implicated as the underlying cause); b) drug-related (drugs implicated as the underlying or contributing cause- multiple cause). Total number not specified
Findings	A 1.3 fold increase (from 6.5 to 10.0) of psychoactive drug-induced deaths based on underlying cause, due primarily to death codified as accidental poisoning by drugs. a 1.5 fold increase for unspecified category 304.9. Annual rates higher for males than for females. A 1.7 fold increase (from 7206 to 14408) of psychoactive drug-related deaths based on counts of underlying or contributing cause. a 7.4 fold increase for non-dependent abuse category and 3 fold increase for drug-dependence category (-->largely due to its being listed as a contributing cause in death from AIDS).
Comments	Methods and criteria used for describing mortality attributed to misuse of psychoactive drugs specified. ICD IX reviewed to select codes for deaths from misuse or abuse of psychoactive drugs

CROSS-SECTIONAL studies

Authors and year (ref. N)	Kaa E, Teige B, 1993 **(48)**
Study site	Aarhus (Denmark) and Oslo (Norway)
Source of data	Institutes of Forensic Medicine
Study period	1980 - 1989
Number of deaths	Fatal poisoning among drug addicts: 238 in Aarhus; 263 in Oslo
Findings	In both samples 80% were males. Increase of annual number of deaths among drug addicts in age groups over 30 years. Only in the Norwegian sample, the increase in the annual number of deaths due to an increase of heroin/morphine related deaths. 48% of deaths in Danish sample due to registered medical drugs (methadone, propoxyphene)
Comments	The definition of "drug addict" applied is specified. The use of the same selection criteria and definition of case in both samples allows for making comparisons. This study does not include all drug-related deaths among drug addicts but only poisoning cases.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Risser D, Schneider B, 1994 **(52)**
Study site	Vienna
Source of data	Institute of Forensic Medicine
Study period	1985 - 1992
Number of deaths	372 drug-related deaths (including: a) narcotic overdoses; b) deaths due to long-term effects of drug abuse; c) suicidal related to drug abuse; d) violent deaths under the influence of drugs; e) medication overdoses; f) deaths of persons registered as drug users)
Findings	Statistically significant increase in drug-related deaths over the years. 68% of deaths due to narcotic overdose; 16% due to medication overdose (illicit use of medication as a drug substitute). Among 230 deceased individuals (categorized as drug injectors) 17.4% HIV+. Morphine and barbiturates detected respectively in 76% and 24% of cases. In 58% of deaths more than one drug was detected
Comments	No ICD codes specified. Drug-related deaths classified according to the definition issued by the Austrian Ministry of Internal Affairs. Definition of drug-related death (in particular in those cases in which death was not connected with actual drug intake) not entirely satisfactory --> possibility of some cases overlooked.

CROSS-SECTIONAL studies

Authors and year (ref. N)	de la Fuente L, Barrio G, Vicente J, Bravo M J, Santacreu J, 1995 **(57)**
Study site	Madrid
Source of data	National Institute of Statistics (for all causes mortality); AIDS Registry (for AIDS deaths related to drug injection); State Information System on Drug Abuse ("mortality indicator") and previous retrospective studies (for acute drug reactions)
Study period	1983-1990
Number of deaths	Estimated rates x 100000 population for each year.
Findings	All of the mortality rates increased from 1983 to 1990 with differences between sex: all causes from 101/100000 to 148/100000, acute drug reactions from 3/100000 to 15/100000 and AIDS from 0 to 20/100000. Drug-related mortality represented 60% of the increase in the rate from all causes in males and 170% of the increase in females
Comments	Four groups of causes of death were considered: all causes, AIDS in injectors, acute drug reactions and drug-related deaths (defined as the sum of deaths from acute drug reactions and AIDS deaths). Mortality rates calculated using as a denominator projection based on the 1981 census and 1991 census. Suicides, acute reactions to drugs other than opiates and cocaine and indirectly related deaths consumption (violent deaths, accident, infections) not included. The characteristics of the sources of data used are described.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Sanchez J, Rodriguez B, de la Fuente L, Barrio G, Vicente J, Roca J, Royuela L, and the State Information System on Drug Abuse (SEIT) Working Group, 1995 **(58)**
Study site	Six major Spanish cities: Madrid, Barcelona, Valencia, Seville, Zaragoza and Bilbao
Source of data	SEIT ("mortality indicator"), pathologists' report of each city's Institute of Anatomy and Pathology (IAF)
Study period	1983 - 1991
Number of deaths	A total of 2596 in the six cities (49,6% in Madrid and 28,5% in Barcelona)
Findings	Increase of the number of deaths between 1983 and 1991(5.6 times among women and 7.3 times among men). The largest absolute increase (rates differences) in Madrid and Barcelona. Male/female ratio 5.9:1. Mean age of deceased from 25.1 in 1983 to 28 years in 1991. Toxicological tests for 53 % of total deaths: opiates found in more than 90% of cases (in 34.3% as a single drug); cocaine almost always in conjunction with opiates (cocaine alone in 0.7% of cases). Increase of polyconsumption throughout the period(heroin/morphine+ benzodiazepines)
Comments	Criteria for case selection and sources of information are described. Deaths from acute reactions to opiates or cocaine defined according two criteria: a) lack of evidence of another cause of death; b) existence of some indication or evidence of recent consumption of opiates or cocaine. Denominators for mortality rates obtained from official census data. The numerators refer to "deaths occurred in" the territory of a city (whether or not the person reside in the territory) while the denominators refer to "person resident in that city". Possible sources of error are specified (errors in identification of cases and the atypical nature of the rates calculated): the result could be a slight overestimation of the mortality.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Hammersley R, Cassidy M T, Oliver J, 1995 **(60)**
Study site	Glasgow and Edinburgh
Source of data	Death reports (not specified). For toxicological analysis: the Department of Forensic medicine and Science Laboratory (for Glasgow) and the Police Forensic Laboratory (for Edinburgh)
Study period	November 1990 - October 1992. Two time periods were compared: November 1990-1991 and November 1991-1992
Number of deaths	66 in Glasgow and 26 in Edinburgh
Findings	The increase in deaths in Glasgow was significant. large number of deaths in Glasgow but were rare in Edinburgh where methadone was associated with most of deaths. Temazepam, diazepam and alcohol associated with most deaths in Glasgow.
Comments	Categories of death included: all sudden and unexpected deaths where the circumstances of death suggested drug injection Drug-related death defined as deaths where drugs were implicated as a cause of death either through circumstance or toxicology. Deaths from infectious diseases and accidents excluded. No details on the characteristics of people died (sex ratio, age distribution ..) are reported.

CROSS-SECTIONAL studies

Authors and year (ref. N)	Torralba L, Brugal M T, Villalbi J R, Tortosa M T, Toribio A, Valverde J L, 1996 **(66)**
Study site	Barcelona
Source of data	Sistema d'Informacio de Drogues de Barcelona (SIDB)
Study period	1989 - 1993
Number of deaths	782 deaths from acute adverse drug reactions
Findings	Deaths among city residents: 79.7%. Mortality rates higher for men than for women (25 per 100000 and 5.8 per 100000 respectively). Mortality rates by age groups group show different pattern by gender. Wide differences between districts and between neighbourhoods in mean annual rates. Although all areas with high adverse drug reactions mortality are areas of low socio-economic level, other areas with similarly low socio-economic indicators do not suffer such high mortality.
Comments	Definition of "deaths due to acute adverse drug reactions (from heroin and/or cocaine)": deaths caused directly by use of these substances (pharmacological overdoses, allergic reactions and toxic reactions to substances added to drugs). Age and sex specific death rates computed using as denominator data from 1991 municipal census. Geographical analysis of mortality at small areas (level districts and neighbourhoods) wad carried out.

REVIEW OF CASE-CONTROL STUDIES

CASE-CONTROL studies

Authors and year (ref. N)	Ruttenber AJ and Luke JL , 1984 **(25)**
Study site	District of Columbia (USA)
Study period and source of data	Records about drug-associated deaths of the Medical Examiner's Office from 1 January 1976 through 31 December 1982 (endemic period: Jan 1976-Dec 1979; epidemic period: Jan 1980-Dec 1982). Columbia Metropolitan Police Department analysed heroin purchased on the street.
Cases	Heroin-related deaths (HRD): 1) deaths with a post-mortem toxicology positive for morphine but with no trauma or natural disease contribution; 2) deaths occurred during hospitalization for effects of documented heroin administration.
Controls	1) General Control group (GC): all deaths due to natural or traumatic causes with either cutaneous stigmata of intravenous narcotic use or positive blood morphine level; 2) Morphine-Positive Control group (MPC): member of the GC group with positive blood morphine levels and no measurable level of any other narcotic drug.
Findings	HRD increased between the second quarter of 1979 and the second quarter of 1982; the population-based mortality rate in 1981 was 17.4 per 100,000 (possibly the highest ever reported). Blood concentrations of both ethanol and heroin can be considered as risk factors for HRD. Moreover, the quantity of heroin in packages sold in the street, its price and the quinine weight per package can be HRD predictors as well. HRD seems to be associated with a casual or recreational use (they were significatively higher during the spring or summer, on Friday or Saturday, from 6 p.m. through 12 p.m.; protective effects of concentrations of heroine in bile)
Comments	Any overdose deaths with toxicological evidence of other narcotics alone or in combination with morphine was excluded in the selection of cases. Comparison with the MPC group adjusts for the possibility that some controls were not active heroin users at the time of death. Analysis of data from autopsy and from street drug composition seems to be useful for identifying new patterns of drug abuse and risk factors for HRD, leading to the identification of prevention strategies.

CASE-CONTROL studies

Authors and year (ref. N)	Davoli M, Perucci CA, Forastiere F, Doyle P, Rapiti E, Zaccarelli M, Abeni DD, 1993 **(43)**
Study site	Rome (Italy)
Study period and source of data	A cohort enrolled for a longitudinal study from 3 Public Treatment Centres in the period 1980-1988 (see Ref. N. 37).
Cases	Overdose deaths (81) among all the deaths in the cohort.
Controls	4 controls for each case (324) were selected among the cohort members still alive at the time of death of the corresponding case, matching on year of birth (+ 2 years) and sex. The variables of interest were considered up to the time of death of the corresponding case.
Findings	High risk of overdose death among subjects who left treatment compared with those still in treatment (OR= 3.55). The highest OR was seen in the first 12 months after drop-out (OR= 7.98). The risk of overdose death was higher among the unmarried compared to married subjects (OR= 2.48). There was a non statistically significant association with lower educational status and younger age at first drug use.
Comments	The selection of controls was made following the 'incidence density' or 'concurrent' sampling procedure, which allows an unbiased estimate of the rate ratio. Exposure of interest were socio-demographic characteristics, pattern of drug use, pattern of treatment. Information on some of these was derived from clinical records and had a limited validity that could account for the lack of association between overdose death and these exposures. A subject was considered retained in treatment when his last contact occurred within 30 days before the date of death or the corresponding date for controls (probably another cut-off point should change the results). It wasn't possible to investigate on concurrent effect of alcohol abuse (information not available), on recreational use of drugs (regular users population) and on comparison with drug users non in treatment (the population came from treatment centres) .

REVIEW OF LETTERS, REPORTS AND EDITORIALS

LETTERS

Authors and year (ref. N)	Reig P, Sanz P, Martì G, Corbella J, 1987 **(28)**
Title	Opioid-related deaths in Barcelona 1981 - 86
Summary	Rapid increase in the number of deaths related to opioids overdose in Barcelona during 1981-86. In this six years 118 deaths (97 males and 21 females) related to possible opioid overdose were recorded in Barcelona. In the same period registered deaths from various toxic substances totalled 354. Opioids were associated with 50% of all the fatal poisonings in 1985 while in 1982 they came third in the list of leading causes of death by poisonings and in 1981 sixth. This change is attributable both to an increase in the number of heroin addicts and to changes in the purity of street heroin, which is influenced primarily by the drug's country of origin

LETTERS

Authors and year (ref. N)	Woody G E, Metzger D S, 1993 **(42)**
Title	Causes of death in injection-drug users
Summary	In the midst of the AIDS epidemic injection-drug users continue to engage in risky behaviour that continues to account for an unacceptably high rate of HIV infection. In a previous longitudinal study the authors found among 415 injection drug-users enrolled, only 5 (18%) deaths from causes associated with HIV disease, although 11 were HIV-positive. The other 82% died from drug-overdoses, homicide, heart disease, renal failure, liver disease, suicide and cancer. Given the immediate threats to their lives, injection-drug users may not share the sense of urgency about wearing a condom, avoiding a used needle, or using proper needle-sterilization techniques: the threat of death from other causes is more imminent. Although physiologic dependence, interpersonal expectations and emotional distress may explain the intractability of risky behaviour among this population, they also highlight the success achieved by those who have increased their use of safe behaviour despite discouraging circumstances

LETTERS

Authors and year (ref. N)	Frischer M, Bloor M, Goldberg D, Clark J, Green S, McKeganey N, 1993 **(45)**
Title	Mortality among drug injectors and notified addicts
Related paper	Frischer et al. J Epidemiol Community Health, 1993 (see cross-sectional Ref N. 44)
Summary	(see ref n. 44) and the number of deaths among drug *addicts* for the whole of the UK (from 1956-66 and from 1976-81) reported by the Home Office Notification Index. Before September 1987 it was not ascertained whether those who were notified injected drugs and, on reflection, it should be avoided making comparisons between the two groups since the UK figures the author cited refer to deaths among notified non-therapeutic *heroin* addicts which are probably not a good surrogate for mortality among injectors. The methodology described in their previous paper was an attempt to circumvent the limitations of reporting mortality in selected groups of injectors, such as those reported to the HONI and enable straightforward comparisons with the general population for a given year. Considering that the average annual number of all-cause deaths in the Glasgow population aged 15-34 years is about 300, the finding of 45 deaths in drug injectors (see ref n. 44) indicates that injecting drug use is strongly associated with an increased risk of mortality in young adults, and is probably responsible for more deaths among this group in Glasgow than any other single factor

LETTERS

Authors and year (ref. N)	Davoli M, Forastiere F, Abeni D D, Rapiti E, Perucci C A, 1994 **(54)**
Title	Longitudinal and cross-sectional mortality studies in injecting drug-users
Related paper	Frischer M et al, 1993 (see cross-sectional Ref N. 44)
Summary	The authors refer to a paper of Frischer et al published in 1993 concerning mortality among drug-injectors, where they reported a mortality from all causes of 54%: this estimate is considered lower than that reported in previous studies (see ref n. 24, 27, 33, 36 and 37) . The main difference between these studies and that of Frischer et al is that the former are all longitudinal flow-up studies, while the latter estimates numerator and denominator separately. The lower rate shown in Frischer's study is not attributable to an underenumeration of the denominator but to the estimate of numerator. In fact over 90% of deaths reported in that study were attributed to overdose and suicide, 2% to AIDS and accidental causes and only 8% to other medical causes. The results from other studies show that the proportion of deaths not directly related to drug use is relevant and injectors have an excess risk for other causes of death. Such an excess risk could have been missed using the sources described by Frischer et al. In conclusion, the only way to measure mortality from all causes in drug-injectors is to carry out longitudinal follow-up studies of defined populations.

LETTERS

Authors and year (ref. N)	Frischer M, Goldberg D, Green S, Bloor M, Clark J, McKeganey N, 1994 **(55)**
Related paper	Letter of Davoli et al, 1994 (see letters Ref N. 54)
Summary	Frischer et al in their replay point out (as done by Davoli et al) that intravenous drug users are a dynamic population with some current users stopping drug use each year, but in the longitudinal study carried out by Davoli et al no information was available about these changes. For this reason Frischer et al consider an alternative method to estimate mortality among injectors using a cross-sectional design (see ref n 44). They found that only 34 of 51 deaths were directly attributable to drug use and the remaining 17 were due to other causes including accidents, suicide by hanging and a variety of medical conditions. While the non-injecting related conditions identified by Davoli et al accounted for 28% of deaths in the italian cohort compared with 10% in Glasgow injectors, the reasons for excess mortality associated with these conditions among intravenous drug users are multifactoril. Thus, there is no logical reason why the mortality for selected conditions in different settings and time periods should be similar. Frischer et al think it extremely unlikely that more than a handful of current injectors who died from medical conditions were not detected in their cross-sectional study. The authors do not accept that "the only way to measure mortality from all causes in drug injectors is to undertake longitudinal follow-up studies of definite populations" (as emphasized by Davoli et al). Longitudinal and cross-sectional methods address related but not identical issues, the complexities of which await further investigation.

LETTERS

Authors and year (ref. N)	Marks J, 1994 **(56)**
Title	Deaths from methadone and heroin
Summary	The UK Home Office Statistical Bulletin reported from 1982 to 1991 243 heroin deaths and 349 methadone deaths. Given that the estimated total addict population in the UK is at least 123500 and taking into account that 40% of notifications (24700 in total) are of addiction to methadone (n=9880), this leaves 113620 addicted to heroin. In 1991, 44 heroin deaths out of 113620 addicts yield a mortality of 1 in 2582; 74 methadone deaths of 9880 give a mortality of 1 in 134. Thus methadone would appear to be 19 times more toxic than heroin. Police surgeon in London find that prescribing of methadone syrup by London's doctors is ineffective in stopping illicit drug use and, worse, the methadone is sold on. Furthermore, methadone produces disturbances of weight , sweating, sleep; and disphoria, in addiction to greater number of fatalities. Given the dangers of methadone and its apparent ineffectiveness, perhaps the current vogue for methadone in the management of addiction should be reviewed

REPORTS

Authors and year (ref. N)	Cherubin C E, 1967 **(2)**
Study site	New York City
Source of data	New York City Department of Health (Narcotics Registry Project) and Office of the Chief Medical Examiner
Study period	1950-1961; 1964
Number of deaths	Number of deaths directly or indirectly attributable to narcotism: 465 for 1950 to 1954,611 for 1955 to 1959 and 1314 for 1960 to 1964 (361 deaths provisionally listed for 1964)
Findings	The disease states associated with addiction to narcotics are reviewed. During the years 1950 through 1961 48% of addict deaths attributed to an "acute reaction to dosage or overdosage". In 1964 this cause of death accounted for 317 of the 361 deaths (87%). 120 deaths were examined by the NY City Medical Examiner's 1950 to 1961 tetanus contributed 8.3% of the deaths of addicts seen by the Office of the Chief Medical Examiner. In this 12-years period endocarditis and sepsis were the causes of death in 8.7% addicts deaths and 2.1% was attributed to tuberculosis. High prevalence of abnormal liver function tests and histologic findings of "small foci of round cell infiltration, particularly in the periportal areas". There is not sufficient evidence to attribute this abnormalities to a viral hepatitis. Glucose tolerance abnormalities and overt diabetes are seen frequently among hospitalized addicts. Overall estimates of 700 to 1000 addicted mothers delivering each year are made by the NY City Department of Health. High prevalence of toxaemia (36%) and of prematurity (47%) by weight.
Comments	This review of conditions associated with narcotic addiction was undertaken to identify gaps of knowledge concerning medical problems likely to arise in any large-scale addict rehabilitation program in a moment when clinical diseases of drug addicts were receiving relatively scant notice

REPORTS

Authors and year (ref. N)	Helpern M, 1972 **(8)**
Study site	New York City
Source of data	Not specified
Study period	1950 - 1970
Number of deaths	1076 from 1950 to 1959 and 4254 from 1960 to 1969
Findings	The greatest number of narcotic deaths occurred in the Borough of Manhattan. Steady increase in fatalities directly caused by narcotic addiction during the last 21 years through 1970. First striking increase in in 1961 (311 deaths). The total number of deaths from narcotism from 1950 through 1959 was 1076 (sex ratio males/females 3.5:1) From 1960 through 1969 there were a total of 4254 deaths. During the 10 years from 1950 to 1959 about 75% of deaths were in individuals under 35 years of age. The average mean age at death from narcotic addiction over the 12 years span from 1950 through 1961 was 29 years; in 1969 was 25 years; in 1970 the greatest number of deaths - 275- was in the age group 20 through 24 and the next to the largest - 179- was in the group between 25 and 29. In 1970 80% of the deaths caused directly by narcotism were from immediate acute reactions and the remaining 20% were caused by complications including sepsi, tetanus, hepatitis and endocarditis.
Comments	The report provides preliminary background information describing narcotic addiction in New York City over the last 40 years. The number of deaths among addicts in NY City are reported from 1950 through 1971. The geographic distribution, characteristics of place of death and pathologic findings are also described

REPORTS

Authors and year (ref. N)	Jansenn W, Trubner K, Puschel K, 1989 **(32)**
Study site	Hamburg and the Federal Republic of Germany (FRG)
Source of data	Federal Criminal Police Office
Study period	1970-1988.
Number of deaths	FRG: steady increase from 1970 through 1979 when 600 deaths were counted; afterwards, deaths decreased to 300-500 annually. In Hamburg the situation was similar except for the last 2 years ('87-'88) when a great increase was observed (1987: 51 deaths, Sep-1988: 50).
Findings	IDUs estimated: 70000-80000. Sex distribution changed from 4.9:1 in 1975 to 2.6:1 in 1985. Mean age increased from 25 to 30. Compared to the other European countries, FRG had the highest number of deaths in the years 1980-86 (400 yearly), followed by Italy (300) and France (200). Death rates varied widely between different region of FRG: the highest were in Hamburg, Bremen and Berlin. In 1986 the mean time of survival was 8.1 years for male IDUs and 6.5 for female. Investigations in Hamburg : almost 100% of dead IDUs underwent autopsy. Cause of death: 70% intoxication; 10% natural death; 20% external violence. 20% were HIV infected; anti-HBs-Ag was present in 42% of the cases. The largest group of intoxications depends on heroin, followed by mixed intoxication (alcohol, barbiturates and benzodiazepine)
Comments	Definition of a drug death (essential for nation-wide analyses): 1) death due to intentional or accidental overdose; 2) death due to long-term abuse of drugs; 3) suicides connected with dependence on drugs; 4) fatal accidents influenced by drugs. The same or similar definition are found in Denmark, Ireland, Monaco and Norway. The association between drug abuse and death is not determined according to the same standards anywhere in the FRG.

REPORTS

Authors and year (ref. N)	Puschel K, 1993 **(46)**
Study site	Hamburg (Germany)
Source of data	Institutes of Legal Medicine Data on HIV-1 prevalence of drug-related fatalities from a multicenter study involving the Institutes of Legal Medicine in the Federal Republic of Germany
Study period	Temporal trend of drug-related deaths in Hamburg showed for the period 1970 - 1991 From 1978 every case of drug-related deaths have been investigated microscopically and toxicologically
Number of deaths	Number of drug-related deaths (DD) reported only for 1990 (n=136) and 1991 (n=184)
Findings	Intentional or accidental overdoses represent about 70-90% of all DD. Since 1988 the number of DD in Germany has increased (1491 in 1990 and 2125 in 1991). The rate of DD per 100000 people differs widely in different regions: high mortality rates can be found in Hamburg, Bremen and Berlin. In 70-80% of the drug victims inflammatory liver changes were found (in 1991: about 35% of serogically investigated DD were HBV positive and about 50% were HCV positive). HIV-1 prevalence rate in Hamburg is the lowest in Germany, less than 5% (the prevalence lies between 0% and 20%). The percentage of acute intoxications by heroin in Hamburg has permanently increased (since 1988, 70-80% of DD due to intoxication with heroin). Combined intoxications with alcohol, barbiturates and benzodiazepines are common
Comments	The definition of drug-related death is specified. Since 1979 drug-related deaths in Germany are registered according to the following definitions: a) death due to intentional or accidental overdose; b) death due to long-term abuse of drugs, i.e. hepatitis, AIDS myocarditis; c) suicides connected with dependence; or d) fatal accidents influenced by drugs

EDITORIALS

Authors and year (ref. N)	Selwyn PA, 1991 **(38)**
Related paper	Perucci et al. Am J Public Health, 1991 (see longitudinal studies Ref N. 37)
Introduction	Increased risk of mortality and morbidity in injection drug users (IDUs) before and after AIDS epidemic. Since the AIDS-era, AIDS-related death increased among IDUs, but overdose increased as well and remains a major cause of mortality. Moreover, drug abuse effects on mortality seem to decline unless multiple causes are considered (standardization of collection, coding and analysis of mortality data are needed).
Comments	Perucci et al. showed, in a cohort of 4200 IDUs attending methadone treatment centers in Rome between 1980 and 1988, an increase in overall and in AIDS mortality. SMR for endocarditis, neoplasm, pneumonia, hearth disease, suicide, cirrhosis also increased. Overdose remained the leading cause of death. Italy and Spain have the highest number of AIDS cases among IDUs: in Southern Europe there was an increasing use of heroin in the late1970s, years of the beginning of HIV introduction; this could led to a rapid HIV spread in the IDUs population. Studies from USA and from Europe suggest that the full spectrum of HIV-related disease in drug users may be underestimated by AIDS surveillance only, because of the increase of mortality from pneumonia, tuberculosis, sepsis, corresponding to high AIDS incidence. Moreover, Perucci et al. observed an increase in occurrence of neoplasms and other malignancies linked to HIV infection, suggesting a role of HIV infection plus use of tobacco and alcohol as risk factors for development of cancer. Existing data on a positive correlation between methadone and retention in treatment and between the latter and reduced risk of health response to AIDS epidemic.

Standardized protocol to assess overall and cause specific mortality rates among drug users recruited in treatment centres in the Member States of the European Union

Introduction

The final task of the EMCDDA project, carried out by the Osservatorio Epidemiologico, was to develop a standardized methodology to assess overall and cause specific mortality rates among drug users in the Member States of the European Union. In order to discuss the major issues to be taken into account for drawing a common protocol to carry out a mortality study in different countries, an expert meeting was organized identifying research groups with experience in planning and conducting cohort studies.

All the Member States of the European Union were informed, through the National Focal Points, about the project and were asked to nominate, if interested, a contact person with experience in this kind of study for attending the meeting. The expert seminar was held at the Osservatorio Epidemiologico in Roma on the 5th and 6th of May 1997 (annex 1: list of participants).

During the seminar each participant presented a brief overview of cohort mortality studies that have been conducted in his country and provided information on availability of the sources of the ascertainment of vital status and causes of death and on accessibility to health records of drug users. General information to evaluate the feasibility for a mortality cohort study and on the characteristics of treatment programs in each country were also gathered through a specific questionnaire (annex 2).

During the seminar the major issues to be addressed and clearly stated in developing a standardized methodology, allowing for temporal and geographical comparisons, were discussed on the basis of the guidelines previously prepared by the Osservatorio Epidemiologico. This protocol was developed according to the suggestions derived from the discussion on each of the following issues:

1. Definition of case
2. Cohort definition
3. Information to be collected
4. Follow-up procedures
5. Cause of death determination
6. Calculation of person-years at risk
7. Calculation of mortality rates

One topic of discussion during the expert meeting, was whether to recruit drug users only in treatment centres or also outside treatment. Even though a conclusive decision was not reached, the most feasible option appeared to be recruitment in treatment centres.

Another topic discussed in the meeting was the opportunity of including in the study only opiates users or also consumers of other types of drugs.

The major issues are:

1) *selection bias*; if treatment centres are used as recruitment sites, which appears the most feasible option, the following consideration should be kept in mind: at present most drug users entering treatment in Europe are opiate users. Non opiate users (cocaine, amphetamines, cannabis, etc) entering treatment represent a very selected group, and mortality figures derived from this sub-population may be highly biased and non-representative of the source population.
2) *power*; in order to detect statistically significant geographical and temporal differences in mortality rates among drug users, a minimum number of drug users should be enrolled in each country. The available figures from characteristics of treatment demand in different European countries, suggest that only opiate users might be considered for this purpose. A detailed analysis of power calculation will be a task of the feasibility study.

Even though the final conclusion has been left to the results of the feasibility study, the following draft protocol deals with the apparently most feasible option of enrolling a cohort of *opiate users "attending" treatment centres*.

1. Objectives

a. To estimate overall and cause-specific mortality among opiates users recruited in treatment centres
b. To analyze temporal trends in overall and cause specific mortality
c. To compare mortality of opiates users among countries

2. Definition of cohort

Both a *retrospective* and *prospective cohort study* will be carried out. The study population will include "incident" and "prevalent" individuals with respect to treatment, enrolled and followed up at variable points in time (*dynamic cohort*). Incident subjects are those starting treatment for the first time or starting a new treatment; prevalent individuals are those already in treatment at the

moment of enrollment.

3. Study population

The study population will consist of a cohort of opiates users (by injection or other routes of administration) who start * treatment at a treatment centre at least once during the study period.

All those clients who have a contact with treatment centres but do not subsequently enter any treatment program, do not have to be enrolled.

The study population will include a retrospective cohort group entering health service centres since ..... to ..... and a prospective cohort component of opiates users entering the same facilities from ..... to ..... .

* Definition of "case" is according to the definition adopted by the REITOX working group (group 3.2) dealing with the improvement of comparability between national treatment reporting systems. For the purpose of treatment demand, the following definitions, "start", "entry", and "demand" are considered synonymous.

4. Inclusion criteria for the enrollment

Inclusion criteria to be enrolled into the cohort are the following:

a. opiates use (by injection or other)

b. starting treatment during the defined recruitment period

c. availability of data for ascertaining vital status

- name and surname (or other identifiers such as social security number)
- date and place of birth
- place of residence (where necessary to ascertain vital status)
- date of entry into treatment centres

For each individual the date on which observation begins will correspond to the date of entry treatment centre: if a subject applies to different centres or refers to a centre more than once during the recruitment period, the date of entry into the study will correspond to the less recent one (when he/she refers to the treatment centre for the first time during the study period).

The date of entry treatment centres will have also to be obtained to distinguish "incident" and "prevalent" cases at the beginning of the study (at the moment of enrollment).

All centres will provide data describing characteristics of the original study population together with the reasons for esclusion.

5. Confidentiality

Each centre will have to adopt specific and effective procedures to ensure the absolute confidentiality of the information gathered. The data on drug users enrolled will have to be managed by a limited number of people, all of whom will be bound by official secrecy. Methods to ensure confidentiality could be proposed and discussed by those centres in which specific procedures have already been adopted and tested.

The identifiers are only necessary to ascertain vital status: all data analysis and reporting will be done without identification of anyone individual's name and drug use status and concomitant health effects.

6. Data collection

A standardized data form will be developed for gathering information from patient records available at the participating treatment centres in order to produce a standard data record structure. The same data form will be used to collect information from both prospective and retrospective cohorts.

The data to be collected from clinical records at health facilities in which the subjects attended will include:

data necessary to assess vital status:

- name and surname or other identifiers such as social security number
- date and place of birth
- place of residence (where essential to assess vital status)

gender

legal nationality

date of entry into treatment centre

type of drug used (the one that currently predominantly maintains the addiction)

route of administration

frequency of use

other drugs used

marital status

educational level

employment status

major occupation

age at first injection (specify: ever/currently)

first treatment ever (yes/no)

scenario of treatment

data on specific laboratory test (HIV, HBSAg, HCV...) performed.

date of last contact with treatment centre

vital status

date of death

cause of death

Another issue discussed in the expert meeting was the opportunity of defining some indicators to be included in the analysis, to take into account the different treatment policies (scenario) of each country, city or center included in the study. It has been suggested to take into consideration the work done for the WHO-multi-city study and other experiences in this field. A specific task of the feasibility study will be to develop an instrument to build such indicator.

7. Feasibility study

The purposes of the feasibility study are:

to define the type of drug user (only opiates users or other) to be enrolled in the study

to identify the recruitment site/s (treatment centres, outside treatment centres)

to develop an instrument to classify each centre included in the study according to the treatment policies and other relevant characteristics to be considered in the analysis

to investigate the availability of data required in the countries and in the centres participating in the mortality study

to develop a standard basic data record structure to be produced by each centre

From each potential participating country should be analyzed:

a. the availability of birth and death registers, or alternative ways of ascertaining vital status of residents and their reliability;

b. the availability of centres recruiting drug users and the possibility of access to health records of drug users at treatment centres;
c. the availability of access to death certificate;
d. the overall expected characteristics of the population of drug users to be enrolled in the study.

8. Follow-up

Each centre will be responsible of ascertaining vital status and cause of death. Follow-up will start for each opiates user enrolled from the time of entry into the cohort (the date of entry into treatment centre) to the end of the study period or to the date of death. There are different options to treat losses to follow-up in the analysis. The more conservative approach consists of assuming losses to follow-up alive at the end of the study period.

The vital status will be ascertained through the population registers of the last municipality of residence at the end of the follow up; if population registers will not be available, different sources of vital status data will be used i.e. national, regional and local mortality registers (in this latter case all subjects not found are supposed to be alive). However, for each country the characteristics of the source and the extent of accuracy of vital status data will have to be described.

The validity of a cohort study depends on complete ascertainment of the events of interest and correct computation of the population at risk. Major accuracy should be put in tracing subjects especially as regards migrant drug users and in limiting the proportion of losses to follow up to a maximum of 5% of the subjects enrolled.

Cause of death will be ascertained through record linkage with general population mortality files, if available, or through death certificate revision. A 90%-95% cause of death determination rate in the study population is a desiderable target.

To compare cause specific mortality among drug users in different countries, coding of the cause of death should be made according to the last revision of the International Classification of Diseases (ICD).

Causes of death will be classified by a nosologist trained in the rules specified by the ICD volumes. A cross-validation study will be also planned as satellite product of the mortality study.

9. Data Analysis

The quality and completeness of each form will have to be checked before the data are entered in a database (the standard structure of the database will be agreed taking into account the essential data to be collected in each centre) for the purpose of correcting errors where possible and of verifying any data not supplied.

Data analysis will include a number of analytic strategies. One aspect of analysis will involve calculation of person-years at risk of dying; each subject will be considered from the date of first enrollment through the end of the study period, or to the date of death or loss to follow up.

- Local analysis

  Direct standardized rates will be calculated for each cohort using as a standard the local population truncated at 15-59 years.

  Standardized Mortality Ratios (SMRs) and their 95% confidence intervals will be used to compare the mortality experience of drug users with that of the national population for the same age, sex and period. The expected numbers of deaths will be calculated using sex and age specific local mortality rates.

- Pooled analysis

  Direct standardized rates will be calculated for each cohort using as a standard the European population truncated at 15-59 years (or the person-years at risk of the pooled cohort) for making temporal and geographical comparisons.

  The analysis of the heterogeneity of mortality could be conducted by using Poisson Regression and including as covariates both individual data and geographical indicators.

TABLES

The following tables summarize the information obtained both during the seminar and through the questionnaire from the experts of European Countries attending the meeting.
In particular table 1 describes the availability of the sources of data to ascertain vital status (on national and local level) and their accessibility.

Table 2 summarizes some information on the feasibility of conducting prospective and retrospective mortality cohort study and on the recruitment of drug users to be followed-up.

TABLE 1a : SOURCES TO ASCERTAIN VITAL STATUS AND CAUSE OF DEATH (AVALAIBILITY AND ACCESSIBILITY)

Country	City	National / local birth registers	National / local death registers	Accessibility to national / local registers	Code of cause of death	Other sources of vital status/cause of death
Austria	Vienna	yes / yes	yes / yes	yes	ICD IX	no
Denmark		yes /	yes /	yes	1969 -1993: ICD VIII 1994 --->: ICD X	no no
France		yes /	yes /	For death registers only anonymous data	ICD IX; from 1997: ICD X	no
Finland		yes /	yes /	yes	up to 1995: ICD IX from 1996: ICD X	Register on hospital admissions Register on post mortem toxicology
Germany	Hamburg	yes / yes	yes / yes	yes	ICD IX (Monocausal understanding)	Drug -related death national registers (police authorities) Documentation by Forensic Institutes (not on national level)
Greece		yes / yes	yes / yes	yes	Certificate of death	no
Italy		yes / yes	yes / yes	yes	ICD IX	

TABLE 1b: SOURCES TO ASCERTAIN VITAL STATUS AND CAUSE OF DEATH (AVALAIBILITY AND ACCESSIBILITY)

Country	City	National / local birth registers	National / local death registers	Accessibility to national / local registers	Code of cause of death	Other sources of vital status/cause of death
Portugal		yes /	yes /	yes	ICD IX	Deaths from overdose at the Forensic Department
Spain	Barcelona (and major cities)	yes / yes	yes / yes	yes	ICD IX	Coroner's registers (all violent deaths)
The Netherlands	Amsterdam	yes / yes	yes / yes	yes, but death register do not provide/have information on cause of death	Hospital records, discharge letters, coroner's report, information from general practitioners	Drug department of the Municipal Health Service Local organization for foreign DUs
United Kingdom		yes /	yes / yes England / Wales	yes		
Ireland	Eastern Health Board Area	yes / yes	yes / yes	yes	ICD IX ICD X: to be introduced in 1998	Coroners' ; police data
Luxembourg		yes /	yes /	yes	No ICD codes (maybe in 1999) Data on death certificate	
Sweden		yes / yes	yes / yes	yes	ICD IX; from 1997 ICD X	no

2TABLE 2a: INFORMATION ON AVAILABILITY OF DATA ON DRUG USERS AND FEASIBILITY OF COHORT MORTALITY STUDY

Country	Accessibility to health record of drug users	Possibility for conducting prospective / retrospective cohort study	Drug users in treatment/not in treatment	Only in methadone treatment	Treatment centres to be included
Austria (Vienna)	yes	? / ?	yes /	yes	Centres for methadone mainten programs
Denmark	no	yes / from 1995	yes /	yes	General practice
France	no	? / no			Specialized centres in drug addiction treatment
Finland	yes (From 1987 Personal Data File Act limits linkage among different registers)	yes / yes	yes / ?		
Germany (Hamburg)	yes	yes / from 1990	yes /	yes	Outpatient's department for drug abuse Psychiatric Department (Hospital) Psychotherapeutic Department for drug abuse Prisons of Hamburg
Greece	yes	yes / yes	Yes / prison	yes	Methadone treatment centre
Italy	yes	yes / yes	yes /		Public Treatment Centres Non Governmental Organizations

TABLE 2b: INFORMATION ON AVAILABILITY OF DATA ON DRUG USERS AND FEASIBILITY OF COHORT MORTALITY STUDY

Country	Accessibility to health record of drug users	Possibility for conducting prospective / retrospective cohort study	Drug users in treatment/not in treatment	Only in methadone treatment	Treatment centres to be included
Portugal	yes	yes / yes	yes / no		Treatment centres for addiction
Spain (major cities)	yes	yes / from 1992	yes / emergency, prison ?		Public non-residential treatment centre
The Netherlands (Amsterdam)	not direct	yes /	yes /	yes	Low threshold methadone mainten programs
United Kingdom	yes	yes / yes	yes / ?		
Ireland	yes	At regional level: yes / yes from 1994	yes / ?		Statutory, drug free; primary care psychiatric services; voluntary + community agencies
Luxembourg	yes	yes / yes; from 1994	yes / ?		Specialized treatment centres (all)
Sweden	no	yes / yes from 1961 to 1995			Inpatient treatment at general and psychiatric hospitals

Annex 1

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Annex 2

Questionnaire for investigating the availability of the data required to carry out cohort study on mortality of drug users in European Countries

1. Name of country .....
   If procedure differs from Region to Region, please fill in one questionnaire for each Region

2. Name of Region .....

3. Are there in your country national birth and death registers?
   yes no

4. Are there in your Region local birth and death registers?
   yes no

5. Could you have access to national or regional birth and death registers?
   yes no

6. How causes of death are codified?
   .....
   .....
   .....

7. Are there in your country or Region other sources of data to ascertain vital status and cause of death?
   yes specify .....

no

8. Could you access to health records of drug users at treatment centres?

   yes no

9. Would you consider feasible to conduct a mortality cohort study in your country (Region)?

   a. prospective yes no don't know
   b. retrospective yes no don't know

10. The cohort could be followed for mortality

    from year to year

11. Indicate the approximate percentage of completeness of follow-up of the cohort anticipated:

    a. for prospective cohort %
    b. for retrospective cohort %

12. What could be the approximate length of time required to obtain the ascertainment of vital status and cause of death?

    months

13. What kind of treatment centres could be involved in the cohort study?

    .....

    .....

    .....

14. What kind of treatment strategies are adopted in treatment centres? (specify the percentage of subjects treated)

    - methadone detoxification programmes

    - methadone maintenance programmes

    - other pharmacological treatments (specify)

      .....

.....

- drug free programmes